

S. HRG. 109-67

FDA'S DRUG APPROVAL PROCESS: UP TO THE CHALLENGE?

HEARING OF THE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS UNITED STATES SENATE ONE HUNDRED NINTH CONGRESS FIRST SESSION ON

EXAMINING FOOD AND DRUG ADMINISTRATION'S (FDA) DRUG APPROVAL PROCESS, FOCUSING ON FDA'S DRUG APPROVAL PROCESS AFTER A SPONSOR DEMONSTRATES THAT THEIR BENEFITS OUT-WEIGH THEIR RISKS FOR A SPECIFIC POPULATION AND USE, AND THAT THE DRUG MEET MEETS STANDARDS FOR SAFETY AND EFFICACY

MARCH 1, 2005

Printed for the use of the Committee on Health, Education, Labor, and Pensions



U.S. GOVERNMENT PRINTING OFFICE
99-761 PDF

WASHINGTON : 2005

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512-1800; DC area (202) 512-1800
Fax: (202) 512-2250 Mail: Stop SSOP, Washington, DC 20402-0001

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

MICHAEL B. ENZI, Wyoming, *Chairman*

JUDD GREGG, New Hampshire	EDWARD M. KENNEDY, Massachusetts
BILL FRIST, Tennessee	CHRISTOPHER J. DODD, Connecticut
LAMAR ALEXANDER, Tennessee	TOM HARKIN, Iowa
RICHARD BURR, North Carolina	BARBARA A. MIKULSKI, Maryland
JOHNNY ISAKSON, Georgia	JAMES M. JEFFORDS (I), Vermont
MIKE DEWINE, Ohio	JEFF BINGAMAN, New Mexico
JOHN ENSIGN, Nevada	PATTY MURRAY, Washington
ORRIN G. HATCH, Utah	JACK REED, Rhode Island
JEFF SESSIONS, Alabama	HILLARY RODHAM CLINTON, New York
PAT ROBERTS, Kansas	

KATHERINE BRUNETT MCGUIRE, *Staff Director*
J. MICHAEL MYERS, *Minority Staff Director and Chief Counsel*

(II)

C O N T E N T S

STATEMENTS

TUESDAY, MARCH 1, 2005

	Page
Enzi, Hon. Michael B., Chairman, Committee on Health, Education, Labor, and Pensions, opening statement	1
Kennedy, Hon. Edward M., a U.S. Senator from the State of Massachusetts, opening statement	3
Clinton, Hon. Hillary Rodham, a U.S. Senator from the State of New York, prepared statement	5
Kweder, Sandra L., M.D., Deputy Director, Office of New Drugs, Food and Drug Administration, U.S. Department of Health and Human Services, Rockville, MD	6
Joint prepared statement of Dr. Kweder and Dr. Woodcock	8
Murray, Hon. Patty, a U.S. Senator from the State of Washington, prepared statement	22
Davenport-Ennis, Nancy, executive director, National Patient Advocate Foundation, Washington, DC; Thomas R. Fleming, professor and chair, Department of Biostatistics, University of Washington, Seattle, WA; David Fassler, M.D., clinical associate professor, Department of Psychiatry, University of Vermont, College of Medicine, and clinical director, Otter Creek Associates, Burlington, VT, on behalf of the American Academy of Child and the Adolescent Psychiatry and American Psychiatric Association; Scott Gottlieb, M.D., resident fellow, American Enterprise Institute, Washington, DC; Abbey S. Meyers, president, National Organization for Rare Disorders, Danbury, CT; and William B. Schultz, partner, Zuckerman, Spaeder, LLP, Washington DC	28
Prepared statements of:	
Ms. Davenport-Ennis	30
Mr. Fleming	36
Dr. Fassler	42
Dr. Gottlieb	51
Ms. Meyers	55
Mr. Schultz	60

ADDITIONAL MATERIAL

Statements, articles, publications, letters, etc.:	
Questions of Senator Murray for the panels	74
Questions of Senator Clinton for Dr. Kweder	75
Response to questions of Senator Enzi by Dr. Kweder	75
Response to questions of Senator Gregg by Dr. Kweder	78
Response to questions of Senator Hatch by Dr. Kweder	78
Response to questions of Senator Kennedy by Dr. Kweder	80
Response to questions of Senator Enzi by Ms. Davenport-Ennis	85
Response to questions of Senator Enzi by Mr. Fleming	87
Response to questions of Senator Kennedy by Mr. Fleming	89
Response to questions of Senator Enzi by Dr. Fassler	90
Response to questions of Senator Enzi by Ms. Meyers	91
Response to questions of Senator Enzi by Mr. Schultz	93

FDA'S DRUG APPROVAL PROCESS: UP TO THE CHALLENGE?

TUESDAY, MARCH 1, 2005

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 9:30 a.m., in Room 106, Dirksen Senate Office Building, Hon. Mike Enzi, chairman of the committee, presiding.

Present: Senators Enzi, Burr, Isakson, DeWine, Hatch, Kennedy, and Murray.

OPENING STATEMENT OF SENATOR ENZI

The CHAIRMAN. I'll call the Committee on Health, Education, Labor, and Pensions to order for the hearing on the "FDA's Drug Approval Process: Up to the Challenge?"

Good morning and welcome to the first in a series of hearings on prescription drugs and the process that is used to ensure their safety and effectiveness.

I strongly believe that Congress needs to engage in strong oversight to help maintain the public's confidence in the FDA. Congress needs to understand the facts before deciding on a course of action. Changes to the drug safety system should be carefully considered to ensure they do not unduly impact patient access to important therapeutics, and benefits and risks must be weighed on the same scale. Separating consideration of safety from consideration of efficacy is the wrong direction to go.

Today's hearing will examine how the Food and Drug Administration, better known as the FDA, makes decisions about new drugs. As we focus on the FDA, we will also take a look at some of the recent controversies that have come to light regarding the drug approval process and the FDA's mission to protect and promote public health.

Our next hearing on Thursday will look in greater detail at the steps the FDA is taking to address public concerns about the safety of our prescription medications. We will also take a glimpse into the future and try to determine if the FDA will be able to handle the challenges the agency will face in the years to come. We are going to look at what the FDA is doing to modernize.

I am not a physician. I am not a lawyer. I am not an expert on biostatistics. But I am a patient. All of us are patients. In fact, I would venture to say that we have all at some point used prescription drugs to maintain or improve our health, and many of us rely

on them on a daily basis. Most of us don't think twice about the work the FDA does every day to ensure that our drugs are safe and effective, or at least we don't think about it until questions about drug safety make the news.

So what is it that we expect of the FDA? At the risk of oversimplifying, I would say that we expect the following. We expect the FDA to approve a new drug only if it is safe, effective, and the known benefits of the drug outweigh the known risks if it is used as intended. We expect the FDA to ensure that companies are communicating the benefits and the risks of their drugs to patients and physicians in a clear and consistent manner. We expect the FDA to keep tabs on the drugs on the market to ensure their continued safety and to take appropriate action if new information demonstrates new risks that were not apparent when a drug was initially approved.

So the questions we as Senators need to ask as we look at the FDA process are the following. Does the FDA properly assess and weigh the benefits and risks of drugs? Does the FDA ensure that information about benefits and risks of drugs are communicated fully? And does the FDA keep appropriate watch over drugs once they are approved on the market? I believe these questions provide the lens through which this committee should focus its attention as we oversee the FDA.

Through holding these oversight hearings, we will bring out the facts beneath the recent controversies so that we can understand whether the FDA's current system worked as intended or whether something broke down. We will learn what the FDA and drug companies did in response to the current safety concerns, whether things should have been done differently, and whether legislation is necessary to address these concerns. We will discuss how the new initiatives that Secretary Leavitt recently announced will further the FDA's effort to meet the expectations that I described earlier. We will also look into whether the FDA and the industry can continue their efforts to reduce drug development time without compromising safety, and whether these steps are steps that Congress and the FDA need to be taking to make that happen.

The past dozen years have brought big changes to the drug approval process. The Prescription Drug User Fee Act, the Food and Drug Administration Modernization Act, and the subsequent amendments to both were bipartisan efforts that brought more consistency, transparency, and accountability to the drug approval process. But it is time for the reevaluation of the FDA's organization and processes. We must not sacrifice safety to speed drugs to the market. However, we must weigh benefits and risks on the same scale.

Every time we take a drug, we take a risk. So we should not overreact to recent events by trying to develop a system that gets us to zero risk. I do have kind of a rule of legislating that I have found over the years to be true, and that is that if it is worth reacting to, it is worth overreacting to, and part of our job is to make sure that we don't overreact but that we appropriately react.

The FDA doctors and patients all have roles to play in evaluating the benefits and risks of a particular drug. But a drug that is unavailable, while it may be safe, can never be effective.

I appreciate Senator Kennedy being here, the other half of the team. Somebody last week asked me what you get when you cross the fourth most liberal Senator with the fifth most conservative Senator and I said, a reasonable bill.

[Laughter.]

The CHAIRMAN. I think that was a Democrat——

Senator KENNEDY. Who is ahead of me?

[Laughter.]

I will wait until the election and I will find out.

The CHAIRMAN. I asked the same question on my side.

[Laughter.]

But I do want to congratulate all the members of the committee for the great job that was done on the genetics nondiscrimination bill, which is now through the Senate. Our job is not finished. We have to get the House version passed and then we have to work out any differences. Hopefully, there will be none. They will recognize the great work that was put into our bill, and the 5 years of effort, and we will get it done.

But I appreciate the bipartisan spirit that the committee has been working on all issues on, and we do have a pretty big plate. I have mentioned that out of the President's top ten priorities, we have 21, so he did combine a few in one or two of his priorities.

At this point, we will have Senator Kennedy make his opening statement and then we will hear from Dr. Sandra Kweder.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. Thank you very much. Thank you, Mr. Chairman. I commend you for calling this very important hearing on the safety of prescription drugs.

When patients go to their medicine cabinets to open a prescription bottle, they deserve an assurance that the medicines that they take are safe and effective. Each one of us relies on the FDA for that assurance.

So I commend Senator Enzi for his leadership in making drug safety a priority for this oversight committee by calling today's hearing. There is no doubt that FDA's ability to assure the safety and effectiveness of medicine is under stress today as never before, and I look forward to working closely with our distinguished chairman on legislation to restore the ability of the FDA to deal effectively with the challenges it faces.

This week's hearings will allow us to examine carefully the issues under consideration for the new legislation. These include better monitoring for drugs already on the market, greater independence for the offices that assure safety, and better protections against improper conflicts of interest on essential FDA panels.

Today's hearing is the first step in the process and I am optimistic it will lead to a comprehensive proposal to make certain that every American can count on the FDA to protect their health.

Obviously, new drugs can pose risks, and the mission of the FDA is to strike the right balance between testing them in advance and withholding them from the market for too long. Since we don't know all the risks in advance, especially long-term risks, FDA has a special responsibility to monitor drug safety after new drugs go on the market.

Last fall, the Food and Drug Administration required anti-depressants, such as Prozac and Zoloft, to be labeled to reflect an increased risk of suicidal thoughts and behavior for children and adolescents. We also began to realize that Vioxx and other drugs in its class increase the risk of heart attack or stroke. The FDA's Advisory Committee last week concluded that these drugs do increase this risk and it made recommendations on how to mitigate the risk of these drugs, which FDA says it will act on soon.

Questions certainly need to be asked about why FDA was reluctant to modify the label on these anti-depressants, especially in cases where they would be used by children.

Hindsight is 20/20, but there is a real concern that the agency may have been too willing on safety issues to protect the pharmaceutical companies instead of the public interest. Why should it take nearly 2 years after the so-called VIGOR clinical trial raised serious questions about Vioxx for the agency to act on the safety risk? And why should it take 5 years to discover that Vioxx, used by tens of millions of patients, may double the risk of heart attack or stroke?

When the drug user fees were enacted in 1992, Congress gave FDA the funds to review drugs much more quickly, and most new drugs in the world are now approved first in the United States, a rather dramatic contrast from the conditions prior to that. But drug safety checks have not kept pace with the speed of drug approval. Inevitably, when new drugs first come to market, we don't know enough about their use by large numbers of patients since clinical trials may not detect a rare but serious problem. Effective FDA oversight after approval is essential to detect problems and the agency needs the resources and the authority to act quickly and effectively to make ongoing assessments of the risks of drugs in use.

It also needs clear authority to require relabeling a drug, if necessary, after approval once a drug is found. Negotiations with a drug maker should never delay accurate information for patients and doctors.

The FDA needs clear authority, as well, to require a drug company to conduct further clinical trials to study a serious safety concern after a drug goes on the market, and it needs a way to enforce these study requirements.

We also need to examine so-called direct-to-consumer advertising, especially when it may lead to excessive use of new drugs whose safety records can't be fully known when they are first approved for use.

The FDA approval process needs to become more open. Conflicts of interest of its Advisory Committee members must be dealt with and fully disclosed in advance to the public when their expertise requires their participation in a study. Many of us were troubled by the reports last week that ten of the 32 members of the Advisory Committee had ties to the drug industry and their votes were decisive in the recommendations that Vioxx and Bextra be allowed to return or remain on the market.

Patients also need better information about drugs written in understandable language so they can understand the risks and the benefits.

I welcome our witnesses today and I look forward to their testimony.

Mr. Chairman, there are only a few good reasons to be absent from your committee meeting, only a few good reasons, but I think Senator Dodd is entitled for his good reason today, and that is he just was the proud father of a baby girl born at 1 a.m. this morning, seven pounds, very healthy. There is no name yet. Enzina, Enzina Dodd has a ring to it.

[Laughter.]

But anyway, I think for all the committee, we wish Senator Dodd and his lovely wife, Jackie, and their marvelous baby girl all the health and happiness in the world. Thank you.

The CHAIRMAN. I know Grace made a tremendous difference in their life and I am sure that the new baby will, as well. It is great to see that family together. That is tremendous news. I appreciate your sharing it with us.

Senator KENNEDY. Thank you very much.

The CHAIRMAN. I would like to submit a statement from Senator Clinton for the record.

[Prepared statement of Senator Clinton follows:]

PREPARED STATEMENT OF SENATOR CLINTON

- I would like to thank Senator Enzi and Senator Kennedy for convening today's hearing on the important issue of drug safety and the approval process at the Food and Drug Administration (FDA).

- In the 1990s, we passed several landmark pieces of legislation that allowed the FDA to considerably shorten the amount of time needed to approve drugs for use by consumers. These changes meant that patients suffering from serious diseases, like AIDS and cancer, could gain quicker access to potentially lifesaving medications.

- While First Lady, I was proud to work with the FDA on developing the Pediatric Rule, which ensures that drugs marketed to pediatric populations have first been tested on children. During my time in the Senate, Senator DeWine and I introduced the *Pediatric Research Equity Act of 2003*, legislation that gave the agency the legal authority necessary to continue enforcing the Pediatric Rule. I also worked with Senators Dodd and DeWine on the *Best Pharmaceuticals for Children Act*, which provides incentives for companies to ensure that their drugs are safe for children.

- For many years, the FDA and its approval mechanisms have been considered the gold standard among the world's drug safety bodies. And no one here doubts the desire of the agency's many employees to continue to carry out its mission of keeping our drug supply safe for all Americans.

- Despite this, we know there have been breakdowns at the agency. We know that, at times, it has taken too long for the FDA to act when a drug may pose a threat to Americans.

- Recent concerns about the safety of drugs that have been approved and are available to consumers point to the need to develop guidelines for ways to monitor drugs once they reach the market.

- Today, we will have the opportunity to hear about the controversies involving both Cox-2 drugs and antidepressant use in

children. These events demonstrate the need to better understand, identify, and monitor the risks that drugs pose after they have been approved for use by the public.

• With my work on both the Pediatric Rule and the *Best Pharmaceuticals for Children Act*, I have tried to encourage both the FDA and drug companies to implement changes to the system in which they test, approve, and market drugs for use in the pediatric population. From these experiences, I know that there are a variety of methods through which we can involve both the industry and the FDA to ensure the safety of products on the market. And I look forward to continuing to work with all stakeholders to improve the safety of our drugs, not just the products marketed to children.

• In addition to further demonstrating the need for post-marketing monitoring, the Vioxx controversy highlights the role comparative effectiveness can play in ensuring the use of the most appropriate treatment for a specific condition. I pushed for inclusion of comparative effectiveness studies in the recent Medicare law, and I would note that one of the first studies to be carried out under this provision is a systematic review of Cox-2 drugs. I believe that this information will assist physicians and patients in selecting the best treatment and help reduce inappropriate uses of treatments that pose unnecessary safety risks to patients.

• I hope that in today's hearing, we can begin to explore the ways in which we can strike a balance between the speed with which we get lifesaving drugs to the market, and the safety that has been, and should remain, a hallmark of the FDA name.

• Again, I would like to thank Senators Enzi and Kennedy for convening today's hearing, and I look forward to working with my colleagues on the HELP committee to developing some practical, bipartisan solutions to continue to ensure that the drugs approved by the FDA are safe for all Americans.

The CHAIRMAN. At this point, I would like to welcome Dr. Sandra Kweder, the Deputy Director of the FDA's Office of New Drugs. Dr. Kweder is a Captain in the Uniformed Public Health Service. Dr. Kweder will review FDA's drug approval process and discuss how approval, labeling, and postmarked surveillance are all considered by the FDA. Dr. Kweder.

**STATEMENT OF SANDRA L. KWEDER, M.D., DEPUTY DIRECTOR,
OFFICE OF NEW DRUGS, FOOD AND DRUG ADMINISTRATION,
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,
ROCKVILLE, MD**

Dr. KWEDER. Good morning, Senators. Thank you very much. I am very pleased to be here today to talk about drug safety and say some words about the drug approval process.

FDA's review of drugs prior to approval and throughout their life cycle on the market is recognized worldwide as a gold standard. We believe that FDA has maintained the highest standards for drug approval, oversight of the investigational process, and for safety in the world.

Like drug development, postmarketing safety, though, is dynamic. While no amount of study before we approve a drug will ever identify all the information about drug effectiveness or risk that there is, our ability to monitor safety has to keep pace with

changes in science as well as with changes in marketing patterns and how drugs are used by doctors and patients.

Acting Commissioner Crawford is committed to strengthening drug safety at FDA. He, in conjunction with Secretary Leavitt, announced new measures to increase public knowledge about drug safety issues just recently. Our goal is to assure that full and rigorous scientific and regulatory judgments are consistently applied to oversight of safety issues at FDA. Our actions will follow Dr. Crawford's announcement last fall of a five-step plan for greater drug safety, but in the coming year, we will also significantly increase our resources devoted to drug safety.

The five-step plan that we announced last fall included a study by the Institute of Medicine of drug safety in the United States, and in particular, FDA's role in assuring that. We have begun planning that with the Institute of Medicine.

Second, a national search for a permanent director of our Office of Drug Safety, and we have begun that process, as well.

We have also implemented a formal process for resolving scientific disputes within our agency among our own scientists, where those exist.

We have begun the fourth point of Dr. Crawford's plan, which was conducting workshops and meetings of our Advisory Committees to discuss complicated safety issues. Our recent meeting on the COX-2 selective inhibitors last week is a very good example of this effort.

And fifth, final publication of three important guidance documents for industry to help companies identify safety issues early and develop effective programs for monitoring them and helping physicians and patients manage those risks. We expect final publication of these guidances this month.

In addition, what was recently announced is that FDA will establish a Drug Safety Board composed of independent senior experts from within and outside the agency to oversee on a routine basis new and ongoing drug safety concerns. This board will also ensure that the public is provided with important emerging information about drug safety issues through modern communication tools, including a drug watch page on the FDA website. Our goal is to provide consumer-friendly information, especially for patients and health care professionals, about emerging risks that they should be concerned about.

As we develop our communications tools, the agency does plan to solicit public input on how we should manage them, make them most effective, and address concerns about disseminating emerging information before we take regulatory action.

In my written testimony, I outline the process of drug development, including how therapies undergo clinical trials under close FDA scrutiny and how sponsors conduct thorough safety and effectiveness analyses, submit applications to the agency, and how we go about the process of exhaustive review of the data unlike any regulatory agency in the world.

But even before FDA approves a drug, the postmarketing monitoring and planning for postmarketing monitoring begins. To do this requires the input of my experts, experts in pre-marketing

safety assessment and in postmarketing safety, so that we can put together a systematic approach to each unique product.

The sponsor, once the product is on the market, must submit periodic safety updates to the agency so that our safety experts can review and analyze adverse event reports. How we respond to information from this ongoing surveillance depends, of course, on the drug's overall safety and benefit profile. When a serious risk is identified, if the public health benefit outweighs the known risks for the intended population in use, FDA allows continued marketing of the drug. We may ask manufacturers to revise the labeling or add new warnings and precautions. We may issue public health advisories and information sheets. We may even consider working with the company to restrict distribution of the product or remove it from the market. Our action depends on the frequency of the reports, the seriousness of the disease, the availability of alternative treatments, and the consequences of not treating the disease if there aren't available treatments.

In 1992, Congress enacted the Prescription Drug User Fee Act. PDUFA, as we call it, emphasizes timely action by FDA but does not alter or compromise our commitment to ensuring that drugs are safe and effective. These fees are essential to our efforts to improve drug safety. The focus on safety begins with the earliest work on drug discovery, and as the drug development process continues, we evaluate the safety of the therapeutic compound in every stage of development. Thanks to PDUFA, we are able to commit far greater resources to these safety responsibilities. Your committee played a significant role in PDUFA, and on behalf of patients, countless patients who have benefited from therapies approved under PDUFA, I want to thank this committee.

In conclusion, at FDA, providing the American public with safe and effective medicines is our core mission. The recent initiatives we have announced will improve our current system to assess drug safety. Moreover, as we strive for continuous improvement, we will evaluate new approaches to advance drug safety. As always, we value input from the Congress, from patients, and from the medical community as we develop and refine our initiatives.

I am happy to take your questions.

The CHAIRMAN. Thank you for your testimony. I appreciate the tremendous summarization you did. I want to assure that your entire statement will be a part of the record. We and our staffs rely on that volume of information to be able to do the job.

[The joint prepared statement of Dr. Kweder and Dr. Woodcock follows:]

JOINT PREPARED STATEMENT OF SANDRA L. KWEDER, M.D. AND JANET WOODCOCK, M.D.

INTRODUCTION

Mr. Chairman and members of the committee, I am Dr. Sandra Kweder, Deputy Director of the Office of New Drugs at the Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss drug safety and the drug approval process.

Because of the importance of these issues, you are holding two hearings over the course of 3 days. Dr. Janet Woodcock, FDA's Acting Deputy Commissioner for Operations, will appear at your hearing on March 3. We have one written statement to address both hearings.

SAFETY IS A HIGH PRIORITY

Let me begin with a few words about safety, and I will return to this issue throughout our written testimony. Modern drugs provide unmistakable and significant health benefits. FDA's drug review process is recognized worldwide as a gold standard. Indeed, we believe that FDA maintains the highest standards for drug approval. There have been significant additions to those standards during the last several decades, in response to advances in medical science. Currently, FDA approves drugs after they are studied in many more patients and undergo more detailed safety evaluation than ever before. FDA grants approval to drugs after a sponsor demonstrates that their benefits outweigh their risks for a specific population and a specific use, and that the drug meets the statutory standard for safety and efficacy. However, no amount of study before marketing will ever elucidate all the information about effectiveness or all the risks of a new drug. Therefore, post-marketing surveillance is extremely important.

Adverse effects that are not detected during clinical trials are identified after approval through post-marketing clinical trials, spontaneous reporting of adverse events, or observational studies based on more widespread use of the product following approval. That is why Congress has supported and FDA has created a post-market drug safety program designed to collect and assess adverse events identified after approval for all drugs we regulate.

This program serves as a complement to the pre-market safety reviews required for approval of prescription drugs in the U.S. FDA also evaluates and responds to adverse events identified in ongoing, post-market clinical trials that test approved drugs for other indications. We also evaluate and respond to events reported by physicians, their patients, or drug manufacturers. With this information, we make label changes and take other regulatory action as needed.

It is important to emphasize that all approved drugs pose some level of risk, such as the risks identified in clinical trials and listed on the labeling of the product. Unless a new drug's demonstrated benefit outweighs its known risks for its intended population, FDA will not approve the drug. However, we cannot anticipate all possible effects of a drug based on data from the clinical trials that precede approval.

NEW FDA INITIATIVES TO STRENGTHEN DRUG SAFETY

November 2004 Five-Step Plan

At FDA, we are constantly striving to improve our processes and methods, and thereby better serve the public health. Recent developments have prompted us to refocus our drug safety efforts and take additional steps to identify drugs that may have unacceptable risk profiles.

On November 5, 2004, Acting Commissioner Crawford announced a five-step plan to strengthen FDA's drug safety program. First, it called for FDA to sponsor an Institute of Medicine (IOM) study to evaluate the current drug safety system. An IOM committee will study the effectiveness of the U.S. drug safety system, with an emphasis on the post-marketing phase, and assess what additional steps FDA could take to learn more about the side effects of drugs as they are actually used. We will ask IOM to examine FDA's role within the health care delivery system and recommend measures to enhance the confidence of Americans in the safety and effectiveness of their drugs.

Second, Dr. Crawford announced that CDER would implement a program for addressing differences of professional opinion. I am pleased to report that CDER recently put this program into effect. Currently, in most cases, free and open discussion of scientific issues among review teams and with supervisors, managers and external advisers, leads to an agreed course of action. Sometimes, however, a consensus decision cannot be reached, and an employee may feel that his or her opinion was not adequately considered. Such disagreements can have a potentially significant public health impact.

In an effort to improve the current process, CDER has formalized a program to help ensure that the opinions of dissenting scientific reviewers are formally addressed and transparent in its decision-making process. An ad hoc panel, including FDA staff and outside experts not directly involved in disputed decisions, will have 30 days to review all relevant materials and recommend to the Center Director an appropriate course of action.

Third, CDER will conduct a national search to fill the currently vacant position of Director of the Office of Drug Safety (ODS), which is responsible for overseeing the post-marketing safety program for all drugs. CDER is seeking a candidate who is a nationally recognized drug safety expert with knowledge of the basic science of drug development and surveillance, and a strong commitment to protecting the pub-

lic health. CDER is working with the Office of Personnel Management on this search.

Fourth, in the coming year CDER will conduct additional workshops and advisory committee meetings to discuss complex drug safety and risk management issues. Most recently, for example, the Agency conducted a 3 day Advisory Committee meeting that examined COX-2 selective non-steroidal anti-inflammatory drugs and related medicines. The Committee held its meeting on February 16–18, 2005, and heard presentations from more than 25 experts. At the end of the meeting, the Advisory Committee issued recommendations that the Agency is promptly and carefully reviewing before taking further action.

Finally, FDA intends to publish final versions of three guidances that the Agency developed to help pharmaceutical firms manage risks involving drugs and biological products. These guidances should assist pharmaceutical firms identify and assess potential safety risks not only before a drug reaches the market but also after a drug is already on the market. FDA expects to publish the final guidances in the second quarter of 2005.

February 2005 Drug Safety Announcement

On February 15, 2005, HHS Secretary Leavitt and Acting Commissioner Crawford unveiled a new, emboldened vision for FDA that will promote a culture of openness and enhanced oversight within the Agency. As part of this vision, FDA will create a new independent Drug Safety Oversight Board (DSB) to oversee the management of drug safety issues, and will improve transparency by providing emerging information to health providers and patients about the risks and benefits of medicines.

Under this proposal, FDA will enhance the independence of internal deliberations and decisions regarding risk/benefit analyses and consumer safety by creating an independent DSB. The DSB will oversee the management of important drug safety issues within CDER. The DSB will be comprised of individuals from FDA who were not involved in the initial review of the drug, as well as medical experts from other HHS agencies and government departments (e.g., the National Institutes of Health and Department of Veterans Affairs). CDER's Deputy Director will serve as the Chair of the DSB. The DSB also will consult with other medical experts and representatives of patient and consumer groups.

FDA will also increase the transparency of the Agency's decision-making process by establishing new and expanding existing communication channels to provide drug safety information to the public. These channels will help ensure that established and emerging drug safety data are quickly available in an easily accessible form. The increased openness will enable patients and their health care professionals to make better-informed decisions about individual treatment options. The Agency is also proposing a new *Drug Watch* webpage that will include emerging information about possible serious side effects or other safety risks for previously and newly approved drugs. This resource will contain valuable information that may alter the benefit/risk analysis for a drug or affect patient selection or monitoring decisions. The web resource may also contain information about measures that patients and practitioners can take to prevent or mitigate harm. This information resource will significantly enhance public knowledge and understanding of safety issues by discussing emerging or potential safety problems even before FDA has reached a conclusion that would prompt a regulatory action. As always, FDA is committed to maintaining patient privacy as it implements these measures.

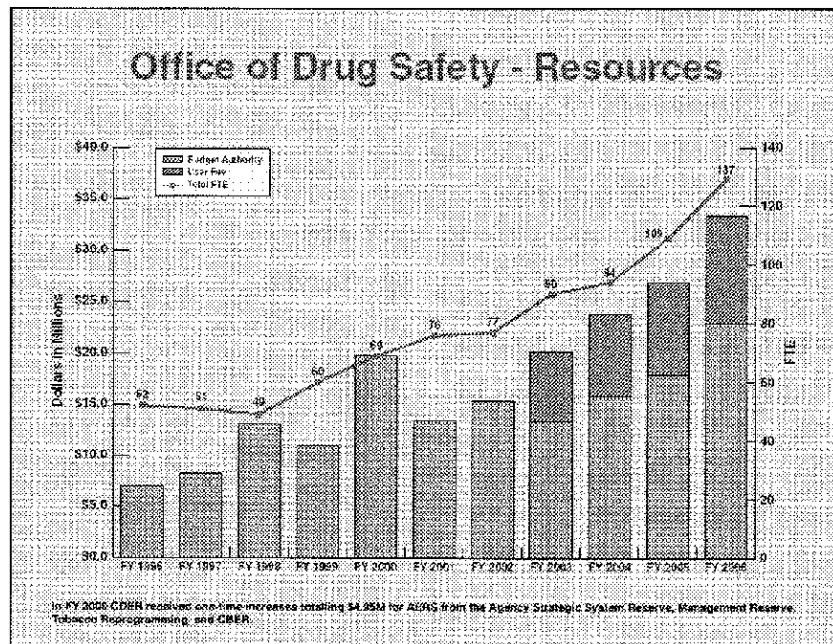
As FDA develops these communication formats, the Agency will solicit public input on how FDA should manage potential concerns associated with disseminating emerging information prior to regulatory action. The Agency will also issue draft guidance on procedures and criteria we will use to identify drugs and information that will appear on the *Drug Watch* webpage. In addition, FDA will actively seek feedback from health care professionals, patients and consumers on how best to make this information available to them.

Increased Funding for the Office of Drug Safety

FDA has a longstanding commitment to provide a strong resource base for ODS. As the graph set forth below demonstrates, we have steadily increased the financial and human resources dedicated to post-market drug safety over the past decade.

The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such

as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. The Administration's proposed budget for ODS will increase by \$6.5 million, including \$1.5 million in user fees, for a total fiscal year 2006 ODS funding level of \$33.4 million. PDUFA resources will represent nearly one-third of the ODS budget for the coming year. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.



THE DRUG APPROVAL PROCESS

Pre-Approval Focus on Safety

FDA's focus on safety begins at the earliest stages of drug development, when we review a product under an investigational new drug (IND) application. During the IND period, products must complete three phases of clinical (human) trials. Phase I studies involve the initial introduction of an IND drug into humans to assess the most common acute adverse effects and examine the size of doses that patients can take safely without a high incidence of side effects. However, before beginning human trials, the sponsor must perform extensive animal toxicity studies. Researchers closely monitor these studies. They may conduct Phase I trials in patients, but often rely on healthy volunteer subjects. In general, these studies yield initial safety data and useful information to establish the appropriate dose of the drug.

Phase II includes the early controlled clinical studies conducted to obtain additional information on appropriate dosing, as well as preliminary data on the effectiveness of the drug for a specific indication in patients with the disease or condition. This phase of testing also helps identify short-term side effects and risks possibly associated with the drug. Phase II studies are typically well controlled, closely monitored and conducted in studies that usually involve several hundred patients. In these studies, researchers compare results of patients receiving the drug with those who receive a placebo, a different dose of the test drug, and/or another active drug. At the conclusion of these studies, FDA and the sponsor meet to determine if the drug's development should advance to Phase III and how to design and conduct further trials.

Finally, researchers design Phase III trials for a larger number of patients and build on the data gained from the first two phases of trials. These studies provide the additional information about safety and effectiveness needed to evaluate the overall benefit-risk relationship of the drug. Phase III studies also provide the basis for extrapolating the results to the general population and provide essential infor-

mation for the package labeling. Once the results of all the clinical trials are available, the sponsor of the application (usually the manufacturer of the product) analyzes all the data and submits a new drug application (NDA) or biologics license application to FDA for review.

Post-Approval Risk Assessment

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA on their drug. Also during this period, we continuously receive adverse event reports through our MedWatch system from other sources such as health care providers and patients. Safety experts review and analyze the reports to establish the frequency and seriousness of the adverse events. Our response to information from this ongoing surveillance depends on an evaluation of the aggregate public health benefit of the product compared to its evolving risk profile. FDA carefully considers the seriousness and the frequency of reported adverse events as well as the estimated number of patients who benefit from the drug. The occurrence of a rare event, even a serious event, may or may not, by itself, be sufficient to take a drug product off the market. Adverse event reports do not solely provide all the data necessary to identify any potential risks that may be associated with a specific product or class of products; however, over time, they provide us with another piece to a complex puzzle.

If the public health benefit of the product outweighs its known risks for the intended population and intended use, FDA allows the continued marketing of the drug. Often, as more becomes known about the potential risks or benefits of a product, its label will be revised so that it better reflects information on appropriate use. For example, FDA may ask the manufacturer to revise the labeling to add information on adverse reactions not previously listed, to add new warnings describing conditions under which the drug should not be used, or to add new precautions advising doctors of measures to minimize risk. FDA often issues Public Health Advisories and information sheets for health care providers and patients that discuss the new safety information. In the event of reports of death or life-threatening injury, FDA and the sponsor may consider restricting the distribution of the product or removing it from the market. Our action will depend on the frequency of the reports, the seriousness of the diseases or conditions for which the drug provides a benefit, the availability of alternative therapy, and the consequences of not treating the disease.

The issue of how to detect and limit adverse reactions can be challenging. How to weigh the impact of these adverse drug reactions against the benefits of these products on individual patients and the public health is multifaceted and complex, and involves scientific as well as public health issues.

STATUTORY CHANGES TO DRUG APPROVAL AT FDA

FDA was founded in response to concerns about safety, and attention to safety pervades everything that we do. In the Federal Food, Drug and Cosmetic Act of 1938, Congress gave FDA the authority to review the evidence that a drug was safe for its intended use. In 1962, Congress added a requirement that drug sponsors also demonstrate that a drug is effective, using adequate and well controlled studies. Thus, drug safety means that the demonstrated benefits of a drug outweigh its known and potential risks for the intended population and use. In recent years, Congress has enacted legislation that provides significant additional tools to improve our focus on safety: the Prescription Drug User Fee Act (PDUFA) and the Food and Drug Administration Modernization Act (FDAMA).

In 1992, Congress enacted PDUFA. This landmark legislation provided significant resources for FDA to hire more medical and scientific reviewers to conduct pre-market reviews, to hire support personnel and field investigators to speed the application review process for human drug and biological products, and to acquire critical information technology infrastructure to support our review process.

In 1997, following the success of PDUFA I, Congress reauthorized the program for an additional 5 years when it enacted FDAMA of 1997. With PDUFA II came higher expectations for product reviews and additional goals designed to reduce drug development times.

In 2002, Congress reauthorized PDUFA for a third time. PDUFA III places great emphasis on ensuring that user fees provide a sound financial footing for FDA's new drug and biologic review process and, for the first time, gives FDA authority to expend PDUFA resources on risk management and drug safety activities during the approval process and during the first 2 to 3 years following drug approval. Mr. Chairman, your Committee played a significant role in creating and reauthorizing PDUFA, and on behalf of my colleagues at FDA and countless patients throughout

America who benefit from the therapies approved under the PDUFA process, I thank you for your efforts.

One of the primary goals of PDUFA was to address the significant delay in U.S. patients' access to new medicines. The objective was to increase benefits to patients, without increasing risks. Before PDUFA, drug lag was a serious concern for U.S. patients and practitioners. Life-saving drugs were available to patients in other countries months and sometimes years before they were available in the U.S. Because of the additional resources and process improvements implemented since PDUFA I became law, the average FDA drug review time has declined by more than 12 months.

It is important to emphasize that a recent study by Berndt, et al. of the National Bureau of Economic Research found no significant differences in the rates of safety withdrawals for drugs approved before PDUFA compared to drugs approved during the PDUFA era. This research confirms FDA's analysis on the same subject. In addition, we are now adding black box warnings sooner than we did before PDUFA. This indicates that PDUFA has been successful in both speeding access and preserving safety.

In general, PDUFA authorizes FDA to collect fees from companies that produce certain human drug and biological products. When a sponsor seeks FDA approval for a new drug or biologic product, it must submit an application accompanied by a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. Before PDUFA, taxpayers alone paid for product reviews through budgets provided by Congress. Under the PDUFA approach, industry provides additional funding in return for FDA's efforts to meet drug-review performance goals that emphasize timelines but do not alter or compromise our commitment to ensuring that drugs are safe and effective before they are approved for marketing.

PDUFA III—GREATER EMPHASIS ON DRUG SAFETY

PDUFA fees are essential to our efforts to improve drug safety. Our trained health professionals work to help ensure and improve drug safety using a process of scientific review, monitoring, and analysis throughout the life cycle of the drugs we approve for marketing. A focus on safety initiates during the pre-marketing phase, when the earliest work on drug discovery begins. As the drug development process continues, we evaluate the safety of the therapeutic compound over a number of years during pre-clinical testing, clinical trials involving humans and eventually, with the submission of an NDA for FDA review. Thanks to PDUFA, we are able to commit far greater resources to our important safety responsibilities.

Under PDUFA III, Congress granted authority for FDA to expend user fees for post-market safety review. FDA made this a top priority during our PDUFA negotiations. Beginning with PDUFA III, for drugs approved after October 1, 2002, we can spend PDUFA resources on "collecting, developing, and reviewing safety information on drugs, including adverse event reports" for up to 3 years after the date of approval. The initiative to address drug safety for PDUFA III products helps FDA better understand a drug's risk profile, provide risk feedback to the sponsors and provide essential safety information to patients and health practitioners.

From October 1, 2002, through December 31, 2004, FDA reviewed 63 risk management plans for drug and biologic products. Twenty-eight of these related to applications submitted after PDUFA III took effect. We also conducted pre-approval safety conferences, risk management plan reviews, drug safety meetings, and meetings with sponsors to discuss proposed drug supplements.

In response to PDUFA III, FDA held a public meeting in April 2003 to discuss risk assessment, risk management, and pharmacovigilance practices. On May 5, 2004, based on the valuable information generated through the meeting process, we published three draft guidances on these important drug safety topics. FDA received extensive comments on these documents, and we expect to publish all three final guidances in the second quarter of 2005.

SAFETY ADVANCES IN FDAMA

Enacted in 1997, FDAMA has been an important addition to FDA's legal framework. FDAMA passed following a thorough Congressional examination of the Agency's policies and programs. It instituted a number of comprehensive changes, re-affirmed the Agency's vital role in protecting the public health and served as the vehicle for enacting PDUFA II.

Pediatric Exclusivity and Safer Use of Drugs in Children

For decades, children were prescribed medications that had not been studied for safety and efficacy in pediatric populations. As a component of FDAMA, Congress provided incentives to sponsors to conduct pediatric clinical trials. Section 111 of FDAMA authorized FDA to grant an additional 6 months of marketing exclusivity (known as pediatric exclusivity) to pharmaceutical manufacturers that conduct studies of certain drugs in pediatric populations. The objective of section 111 was to promote pediatric safety and efficacy studies of drugs. With the valuable information generated by these studies, the product labeling can then be updated to include appropriate information on use of the drug in the pediatric population. To qualify for pediatric exclusivity, sponsors must conduct pediatric studies according to the terms of a Written Request issued by FDA and submit the results of those studies in an NDA or supplement.

In 2002, Congress renewed this authority when it enacted the Best Pharmaceuticals for Children Act (BPCA). BPCA also mandates that FDA report to the Pediatric Advisory Committee, in a public forum, any safety concerns during the 1 year period after we grant pediatric exclusivity. To date, we have reported safety concerns on 34 drugs at six separate public advisory meetings.

Finally, BPCA contains important, new disclosure requirements. Outside of BPCA, the Agency generally may not publicly disclose information contained in an IND, unapproved NDA, or unapproved supplemental NDA. Once FDA approves an NDA or supplemental NDA, the Agency can make public certain summary information regarding the safety and effectiveness of the product for the approved indication.

However, section 9 of BPCA gives FDA important new disclosure authority. BPCA requires that, no later than 180 days after the submission of studies conducted in response to a Written Request, the Agency must publish a summary of FDA's medical and clinical pharmacology reviews of those studies. Moreover, we must publish this information regardless of whether our action on the pediatric application is an approval, approvable, or not-approvable action. Thus under FDAMA, information on pediatric studies conducted in response to Written Requests was not available until after the supplemental application was approved. In contrast, under BPCA, a summary of FDA's medical and clinical pharmacology reviews of pediatric studies is publicly available regardless of the action taken on the application. Since 2002, FDA has posted the summaries of these reviews for 41 products submitted in response to a Written Request on FDA's website at: (<http://www.fda.gov/cder/pediatric/Summaryreview.htm>). This information provides a rich source of valuable safety information to allow pediatricians to make more informed decisions about whether and how to use these drugs in their patients.

Post-Marketing Safety Studies

On April 30, 2001, FDA's regulations implementing section 130 of FDAMA, which requires sponsors of approved drugs and biologics to report annually on the status of post-marketing commitments, became effective. These regulations modified existing reporting requirements for NDA drug studies and created a new reporting requirement for biologic products.

FDA may request that the sponsor conduct post-marketing studies to provide additional important information on how a drug works in expanded patient populations or to identify safety issues that occur at very low frequency or in special patient populations. The post-marketing safety study obligations in section 130 are of keen interest to patient and consumer advocates who track the completion of post-marketing commitments and FDA's efforts to review study results and modify drug labeling. The regulations implementing section 130 provide FDA with a mechanism to monitor study progress through the annual submission of study status reports. FDA posts the status of post-marketing studies on its public website and publishes an annual summary of industry's progress in fulfilling post-marketing commitments in the *Federal Register*.

CRITICAL PATH

On March 16, 2004, FDA released a report addressing the recent slowdown in innovative medical therapies submitted to FDA for approval: "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." The report describes options to modernize the medical product development process to try to make it more predictable and less costly. The report focuses on ways that FDA could collaborate with academic researchers, product developers, patient groups, and other stakeholders to make the critical path much faster, predictable, and less costly.

Enhancing the Safety of Medical Products

During drug development, safety issues should be detected as early as possible. However, because of limitations of current methods, safety problems are often uncovered only during clinical trials or, occasionally, after marketing. Despite efforts to develop better methods, some tools used for toxicology and human safety testing are outdated. Clinical testing, even if extensive, often fails to detect important safety problems, either because they are uncommon or because the tested population was not representative of eventual recipients. Conversely, some models create worrisome signals that may not be predictive of a human safety problem.

There are opportunities for developing tools that can more reliably and efficiently determine the safety of a new medical product. To meet this challenge, FDA has called for a new focus on modernizing the tools that applied biomedical researchers and product developers use to assess the safety and effectiveness of potential new products. Many of these tools—diagnostics such as pharmacogenomic tests and imaging techniques—would also be used after marketing to monitor safety in the real world clinical setting. The Critical Path report describes opportunities for FDA, working with academia, patient groups, industry, and other government agencies, to embark on a collaborative research effort. The goal is to create new performance standards and predictive tools that will provide better answers about the safety and effectiveness of investigational products, to do this faster and with more certainty, and to enhance the safety of these products in the clinic.

In addition to improved safety tools, Critical Path also focuses on tools that will help individualize therapy. We enhance safety when the target population does not include individuals who cannot benefit from the treatment. For these individuals, drug exposure is all risk. Better tools for individualized therapy will help to identify patients who will respond to therapy. New science has provided the basic knowledge to make these tools a reality.

Critical Path is not a fundamental departure for FDA, but rather builds on the Agency's proven "best practices" for expediting the availability of promising medical technologies. While the report touches on all aspects of medical product development, identifying new tools to address drug safety challenges would represent a giant step down the Critical Path.

CONCLUSION

At FDA, providing the American public with safe and effective medical products is our core mission. We base decisions to approve a drug or to keep it on the market if new safety findings surface on a careful balancing of risk and benefit to patients. This is a multifaceted and complex decision process, involving scientific and public health issues. The recent initiatives we have announced will improve our current system to assess drug safety. Moreover, as we strive for continuous improvement, we will continue to evaluate new approaches to advance drug safety. As always, we value input from Congress, patients and the medical community as we develop and refine these drug safety initiatives.

Once again, thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.

The CHAIRMAN. I do want to mention that we are trying to be very thorough in the hearing so that we can get as much information as possible before we draft the bill. We are trying to have some restraint, and, of course, I am calling on all committee members to do that, and so far, we have had success with that.

Getting back to your testimony, could you describe the vetting process the FDA uses for Advisory Committee members in general? Were there any additional criteria for selecting members for the Advisory Committee that examined the COX-2 inhibitors?

Dr. KWEDER. The process for vetting—for members' participation for an individual meeting is extremely complicated and we have a whole section of our website devoted to all the rules and regulations that are required to be met. We can get that information for you.

I will tell you that one of the things that makes a potential participant a valuable member of any expert committee is their experience in drug development, drug safety assessment, as well as clini-

cal practice. Oftentimes, it is research experience. Most medical researchers in this country have at one time or another had funding from—participated in funding from a pharmaceutical company.

In the case of this recent meeting, we had the unusual circumstance of reviewing six COX-2 inhibitor products marketed and not marketed by four different companies, as well as over 30 non-steroidal anti-inflammatory drugs from numerous different companies. There was almost not a drug company in the world that someone didn't have to be screened for having an interest in for this particular meeting. Our advisors and consultant staff are experts in that and we think they did a very good job in screening people for important conflicts of interest.

The CHAIRMAN. Thank you. Changing it slightly here, the FDA recently published a report on the performance of drug and biologic firms in conducting postmarketing studies. The report indicates that of the studies concluded between October 1, 2003, and September 20, 2004, no studies were identified where the commitment was not met. Likewise, the study indicates that only one percent of the pending studies for drug applications were delayed.

In your opinion, does this report indicate that pharmaceutical firms are meeting their postmarketing study commitments in a timely manner?

Dr. KWEDER. To the extent the data tells us that, I think that things have improved significantly. The number of postmarketing study commitments that were completed in fiscal year 2004 was double that number from 2003.

The CHAIRMAN. Thank you. We have heard that the FDA determines safety using a risk-benefit analysis. Can you explain what factors the FDA considers in its risk-benefit analysis, and in your opinion, is it ever appropriate to assess the safety of a drug product without weighing both its risks and its benefits?

Dr. KWEDER. Let me start with the last question. I think it is never appropriate to look at only benefit or only safety. There is always a judgment.

First, let me say that the first thing we look at is what is the risk itself? Is the risk or the safety concern something that is an annoyance or is it something that is significant and important? Is it an itch that will go away, or is it liver failure? Those are very, very different considerations. So what is the risk?

How common is the risk from what we can tell? Does it occur in one in 100 people or one in five million?

We look at what is the product—what is the disease or the condition being treated? Again, is it an annoyance or is it something important? So what the disease is it is treating is an important consideration.

We look at how beneficial is the drug? What do we understand about if this drug were not available, what are the alternative treatments that might be available? How good are they?

We also factor in how certain we are of the risk, given all of those other considerations, and if the disease were not treated, particularly for something which there is no alternative therapy available, what are the consequences to the patient of that?

In order to make these kinds of assessments, it really takes expertise from a number of different people, experts who understand

how benefit was determined in the first place and what those studies showed. It also takes expertise from people who think about drug safety data in the grand scheme of the population and how certain we are depending on how a risk was detected and what other sources of information might be able to help us. And it really also takes the important perspective of experts who understand how medicines are used by doctors and patients and the consequences of taking a product off the market compared to having choices available on the market.

These are tough decisions. If there was a magic formula, our job would be easy, and honestly, I probably wouldn't work at FDA. It wouldn't be interesting. And people are always looking for, what is the magic equation? There just isn't one and it takes—no one person makes a decision. Someone has to take responsibility, but it takes lots of people coming to the table with different perspectives and expertise to decide what to do.

The CHAIRMAN. You mentioned that no one person can make the decision, and, of course, it isn't one person. There has been discussion about having a separate safety approval oversight from the original drug approval. In light of what you just said on the process, is it possible to have those as two distinct, separate entities? Will not the safety hold up the approval—

Dr. KWEDER. Sure.

The CHAIRMAN. And approval hold up the safety?

Dr. KWEDER. I actually can address that. I have been at FDA a long time. I graduated from college when I was 12.

[Laughter.]

I actually spent 2 years in the early 1990s as the Director of what is now our Office of Drug Safety. So I have had the opportunity to work, spending most of my day thinking about safety issues and postmarketing surveillance, as well as from the drug development side.

In fact, our Office of Drug Safety is independent. It is a completely separate office from the Office of New Drugs that does the pre-market reviews. On the other hand, having those in the same Center is one of the most important things that we can do to ensure that we are communicating and have a full understanding of risks and benefits and the judgments that ultimately have to be made about what would happen with a product.

The CHAIRMAN. Thank you. At this point, I am going to turn over the gavel to Senator Burr, who will continue here, because I have to go see a buffalo about a nickel. I will be back.

Senator KENNEDY. Senator, I want to tell you, I can give you a report on your buffalo. I just saw the buffalo outside of the Russell Building, and behaving reasonably well to date, so I am sure he is waiting for your appearance.

[Laughter.]

The CHAIRMAN. That is because he is from Wyoming.

[Laughter.]

Senator BURR. [Presiding.] I thank the chair and encourage the chairman not to wrestle that buffalo.

[Laughter.]

Dr. Kweder, welcome. Thank you for your testimony.

Dr. KWEDER. Thank you.

Senator BURR. At this time, the chair will recognize Senator Kennedy for questions.

Senator KENNEDY. Thank you very much, Mr. Chairman.

The failure to recognize the safety problems with the COX-2 drugs may have resulted in tens of thousands of patients suffering heart attacks or strokes and an unknown number of deaths. Can you assure the committee and the American people that this kind of lapse will never happen again?

Dr. KWEDER. Senator, we were concerned about the potential safety risks of the COX-2s, and in particular, Vioxx, from the time the first application came in. We held specific public meetings to discuss those risks with experts. When the first data suggesting that there was a risk came out in a clinical trial in 2000, shortly thereafter, when we had had an opportunity to review the data, we held another expert Advisory Committee, including expert cardiologists and gastrointestinal experts and a number of other safety experts to address specifically what reactions we should take in order to determine whether that risk was, indeed, as what it seemed to be from that one clinical study.

So our actions following that were to work with the company as the committee asked us to do to try and further investigate this potential risk, which we did, through clinical trials, as well as to label the product for—to assure that clinicians in practice would understand that the risk existed.

I would say that the lapse from my perspective was the delay that it took to get that information into labeling—it took over a year—as well as once it was in labeling, the failure of that information somehow to be in the forefront of the consciousness of the prescribing clinician.

Senator KENNEDY. This goes back to 2000. As I understand, I think Dr. Crawford told me it was Merck that called Dr. Crawford and indicated they were the ones that were going to take it off the market.

Dr. KWEDER. In 2004?

Senator KENNEDY. Yes.

Dr. KWEDER. What happened was the—

Senator KENNEDY. I mean, we are trying to find out. I don't want to use all my time here, now—

Dr. KWEDER. Yes. No, they did—

Senator KENNEDY. Doing a case study on it.

Dr. KWEDER. It was one of the studies—

Senator KENNEDY. This is enormously important and significant.

Dr. KWEDER. Absolutely.

Senator KENNEDY. There is a lot of time lag. We understand that you can't press buttons in terms of clinical trials and review, but I think there is this time lag and we want to try to make sure that this kind of challenge isn't going to happen again, that the steps are being taken in the Department.

Dr. KWEDER. Absolutely.

Senator KENNEDY. Maybe you could give us some analysis about how we can correct the delay—

Dr. KWEDER. Yes. I think one of the ways that—

Senator KENNEDY. And hope that we can assure that the FDA's intentions to address the safety issues are going to work.

Dr. KWEDER. Yes.

Senator KENNEDY. That is what we are interested in and I would be interested if maybe you could submit some information to give us those kinds of assurances.

For most people who took the COX-2 drugs, it didn't work any better than the older, cheaper drugs that are much safer. So why were so many people taking the COX-2 drugs when there doesn't appear to be much of a medical need for them to do so? Was this the pressure from direct-to-consumer advertising? Were there inducements to doctors to prescribe them? Are there other drugs on the market right now that patients are being induced to buy and that doctors are being induced to prescribe through clever advertising or high-pressure sales?

Dr. KWEDER. I can't—I certainly don't know what inducements there were for doctors to prescribe them. I think as a physician and as a member of this society, we always tend to think that new must be better, which is certainly not the case, and the company was never, ever allowed to make claims that they were better, at least in terms of how effective they were.

Several of the reasons that they may have been used more often is because they are, for the most part, once a day or twice a day, where the older drugs are required to be taken many times a day, and also because there was a great hope that these would have fewer side effects and people would be able to tolerate them better without the stomach upset that some of the other products may have carried.

There certainly was a great deal of marketing, both to health care providers and to consumers, of these drugs.

Senator KENNEDY. You indicated in response the follow-up that is being done by various drug companies, and I think you had indicated that there were two times as many responses as there were in 2003.

Dr. KWEDER. Yes.

Senator KENNEDY. As I understand it, we have different kinds of reports. We have one where we have an adverse reaction and we have another whether the drug companies are going to have to do the clinical trials about safety issues.

You say that the manufacturers are required to submit periodic safety reports to the FDA about drugs, and yet, generally, as I understand it, the FDA has no authority to require the companies to perform safety trials after approval. Is that right?

Dr. KWEDER. Yes, I think—and you are talking about two—there are two different things.

Senator KENNEDY. That is right.

Dr. KWEDER. Yes, that is correct.

Senator KENNEDY. If you could—

Dr. KWEDER. That is correct.

Senator KENNEDY. Spell out those two different requirements, what you have authority for and the degree of cooperation—

Dr. KWEDER. Sure.

Senator KENNEDY. And what you don't have authority for and whether you think you ought to have the authority.

Dr. KWEDER. OK. First, the safety reports. Companies are required by law to submit to us reports on all new information they

have about the safety of their products—adverse reactions that are reported to the company, most of which are reported to companies, new studies that have something to say about the safety of their product, maybe that weren't done by them but were done by somebody else. That information regarding safety must be submitted on a periodic basis to the agency.

For important safety issues, like really severe or life-threatening events, those reports come in all by themselves in a very short period of time. They are called 15-day reports. But also on a periodic basis, companies are required to give a comprehensive assessment of their safety, usually through annual reports, or actually more often quarterly reports for the first 3 years of marketing.

That is separate from any requirements they have to actually conduct specific studies of postmarketing safety, such as an additional randomized clinical trial or an epidemiology study that we might ask them to do. We don't have the authority to tell them, you must do this particular trial. That is an authority we don't have.

Now, we certainly have a fair amount of influence in convincing them to do some of these studies, and we are, for the most part, reasonably successful. But we don't have the authority to say, you must do the trial.

Senator KENNEDY. My time is up. I would like to get into this area in a little greater detail about whether this could be very important authority that could enhance the kind of safety issues. If I could just have 15 seconds more, Mr. Chairman.

Senator BURR. I yield to the gentleman.

Senator KENNEDY. I think there is a reasonable question where people would say, shouldn't we buttress inside safety and give all authority there to the FDA—rather than having an outside Advisory Committee. But as I understand, your point is that there are basically two different functions and that the public is best served by having two different functions, one within FDA that is going to deal with the various technical, clinical aspects in terms of safety, and then having an outside group that takes a de novo view of it and makes an independent evaluation of the issue.

Dr. KWEDER. That is actually what we are proposing in our program, is to have an independent board of inside and outside people to oversee the process, which we think will be very helpful.

Senator BURR. The Senator's time has expired and the chair would recognize Senator Hatch for questions.

Senator HATCH. Welcome to the committee.

Dr. KWEDER. Thank you, sir.

Senator HATCH. I am happy to see you again.

Dr. Kweder, as the senior member of the Senate Finance Committee, I had the opportunity at a hearing you testified at last year on drug safety issues. One question I would like to pose to you is this. Isn't it true that all pharmaceutical products have, to some degree or not, a degree of risk?

Dr. KWEDER. Yes, sir, it is true.

Senator HATCH. In your testimony, you State that the FDA, quote, "grants approval to drugs after a sponsor demonstrates that their benefits outweigh their risks for a specific population and spe-

cific use and that the drug meets the statutory standard for safety and efficacy," unquote.

Would you just please go into a little more detail with regard to the statutory standard for safety and efficacy?

Dr. KWEDER. Well, I won't go into too much detail, but—

Senator HATCH. We could spend all day on that.

Dr. KWEDER. We could spend all day on that. In general, while a product is in development, we are working with the company to define what it is that would show that a drug works. What is its intended use? And based on what the company thinks or it looks like the drug would be useful for, how to do the studies to show that that use is beneficial. And companies spend a great—and the experts that they work with, as well as the agency, spend a great deal of time carving that out for a particular product and a particular clinical need.

As those studies are being developed, we are also looking very carefully at what the risks of the drug might be. We have some clues from animal studies, but they never tell us the whole story. And ultimately, given the benefit that might be there, does the drug have a reasonable balance of safety?

You know, you can take the same drug that might be being studied to treat a minor annoyance condition—let us just pick something, tension headaches—and that drug turns out in clinical studies to have a risk of liver failure. The same drug is also being studied to treat people with strokes, okay, and it has a benefit in prolonging life in people with strokes, but it has this same liver toxicity because that is inherent in the drug. But it is so remarkably effective in preventing mortality with strokes, we might say—this is all hypothetical—that the liver risk is worth it because the benefit is enormous in that population of patients. However, risk of liver failure is completely unacceptable no matter how effective this drug is in treating people with tension headaches because tension headaches go away on their own.

Senator HATCH. Yes.

Dr. KWEDER. So, those are the kinds of judgments that we have to make.

Senator HATCH. Do you know of any drug that has been approved by FDA that is risk-free?

Dr. KWEDER. None that I am aware of.

Senator HATCH. I am not aware of any, either.

Now, I would like to discuss the postmarket drug safety program. In your testimony, you talk about the FDA evaluating and responding to events reported by physicians, their patients, or drug manufacturers. How many times per month or per year is the FDA contacted by individuals who want to report adverse events, and how do you get the word out to people that they are to report these events to the FDA?

Dr. KWEDER. We receive about 400,000 spontaneous reports of adverse events a year, and that is a growing number. We get a growing number of reports. We always need more.

One thing that we know is that when there are programs to actively encourage reporting, we get more reports. When we launched the MedWatch program back in the early 1990s, the number of reports—which was really kind of a public awareness campaign to

encourage reports—our reports improved and the quality of them improved.

We try as best we can to encourage reporting through drug labels, any public health announcement that we do, but we always need more. There are a lot of barriers to reporting. We have tried to address some of those by making it easier for people to report, by making it simpler and more convenient, but we can always use more.

Senator HATCH. I want to commend the FDA for initiating the five-step plan to strengthen the FDA's drug safety program. You mentioned the Institute of Medicine study to evaluate the current drug safety system. When will that study be done?

Dr. KWEDER. We have actually begun planning with the Institute of Medicine. We expect the study to begin—my understanding is that it won't be for another 6 months for them to obtain a panel of experts to begin the process.

Senator HATCH. Thank you. My time is up, Mr. Chairman.

Senator BURR. I thank the Senator.

Senator Murray for questions?

Senator MURRAY. Thank you very much, Mr. Chairman, and I would ask unanimous consent to put my statement in the record, my opening statement.

Senator BURR. Without objection.

[The prepared statement of Senator Murray follows:]

PREPARED STATEMENT OF SENATOR MURRAY

Mr. Chairman, I want to thank you for scheduling these important FDA drug safety hearings.

As the committee of jurisdiction over FDA, it is imperative that we have a better understanding of the challenges facing the FDA approval and the post-market surveillance process. These hearings are an important first step in determining what legislative remedies are necessary to protect the integrity of the FDA drug approval process, as well as the integrity of this process. We also owe it to the millions of patients who depend on the FDA to protect their health and safety.

Back in 1997, when I was a new member of this committee, one of the challenges I faced was reauthorization of PDUFA and FDA modernization and reforms. It had become clear that unnecessary bureaucratic delays were jeopardizing access to new life-saving drugs and therapies. Unnecessary and burdensome regulatory processes were also adding to the cost of new drugs and treatments. FDA needed additional resources and authority to meet the challenges of new biotech and biomedical advances. However, it was imperative that we did not jeopardize the underlying public health mission of the FDA.

Striking that balance and developing real reforms that improved performance, and that reduced unnecessary delays, was a difficult task. This committee has a long tradition of working in a bipartisan manner to develop real, effective solutions for improving FDA. I look forward to working with the Chairman in developing necessary remedies to protect the FDA drug approval process and in restoring greater patient confidence in this process.

I want to thank today's witnesses, and I am particularly pleased to welcome to this committee Dr. Thomas Fleming, Chairman of the Department of Biostatistics at the University of Washington.

Dr. Fleming served on the Drug Safety and Management Advisory Committee that recently met to discuss the status of Vioxx and other COX2 drugs. He brings to the HELP Committee 28 years of experience in collaborating on clinical trials and has nearly 20 years of service on FDA Advisory Committees. I appreciate his willingness to testify and offer his insights into what actions Congress and the FDA need to take to protect the public health.

I really appreciate having this hearing today. I think it is really important that this committee focus on how we can better understand the challenges before FDA and determine what legislative remedies are necessary. So I appreciate the hearing today.

I especially want to thank Dr. Thomas Fleming, who is the Chairman of the Department of Biostatistics at the University of Washington, who will be testifying in the next panel. He has served on the Drug Safety and Management Advisory Committee that met to discuss Vioxx and other COX-2 drugs and brings 28 years of experience in collaborating on clinical trials and 20 years of service on FDA Advisory Committees, so I really appreciate him traveling here and look forward to his testimony.

But Dr. Kweder, I did want to follow up on Senator Kennedy's question because I think it is important that we understand what the current process is and if there are problems with it, what we need to do legislatively. He asked you about the FDA clinical trials that Merck shared with you, the clinical trials on Vioxx, and I think it was 2002 when the larger study was done on Alzheimer's patients that was given to you and you said there was a delay in getting a warning on labels after that. What caused the delay?

Dr. KWEDER. Well, what caused the delay is that we don't have the authority to tell a company, this is how your label has to look. This is the language that needs to go into your label. Here is where it goes, end of story. We have to negotiate with the company the specific language of how things should be worded, placement, those kinds of things, and—

Senator MURRAY. So you were talking to them and making—

Dr. KWEDER. Correct.

Senator MURRAY. Did they reject that warning? Did Merck reject the warning?

Dr. KWEDER. You know what? They rejected many of our proposals, and we similarly rejected many of the proposals—most of the proposals they sent to us.

Senator MURRAY. Does FDA need authority, in your opinion, to change labeling?

Dr. KWEDER. I think that stronger ability to require changes in labeling would be very helpful.

Senator MURRAY. On the clinical trial issue, FDA cannot order a company to do a clinical trial, is that correct?

Dr. KWEDER. That is correct.

Senator MURRAY. Is that something that would, if you had broader authority on that—

Dr. KWEDER. I think that we actually have a fair amount of influence over getting a company to do a clinical trial. There are cir-

cumstances where being able to require it would be very helpful, but I think those are not on a daily basis. It would be under extreme circumstances.

Senator MURRAY. So some kind of authority based on some premise would be helpful, or do you want broad authority? What are you thinking?

Dr. KWEDER. Well, I think that is something that would need much further discussion about what the limits of that might be.

Senator MURRAY. How about changing labels? You don't have the authority to change labels, correct?

Dr. KWEDER. We do not have the authority to require a specific label change. Most of the time, I have to say, the discussion with companies about changes in labels doesn't take as long as it took for that particular one. Usually, you know, it is just a matter of a few back-and-forths and just getting the language right and making sure it is clear. It is usually not a problem.

Senator MURRAY. How about ordering a company to withdraw a drug? Do you have that authority?

Dr. KWEDER. We have the authority—the authority that we have—the specific authority we have is much more convoluted than that, but when we tell a company that we think their product needs to be withdrawn, that is usually not an issue. It usually happens pretty readily. And usually, the circumstances are such that the company is in agreement. If the FDA goes forward and says to the public that we think a drug should be withdrawn, the handwriting is on the wall.

Senator MURRAY. OK. Does FDA have other steps it can take to alert the public to any kind of—

Dr. KWEDER. Actually, one of the things that we are—we have some. We can issue public health advisories. One of the proposals that Secretary Leavitt announced last week was that we would develop what we would call a drug watch page, where we would advise the public of new, ongoing, emerging safety issues as well as things that we are concerned about, because putting things into a label does take time. Even if we come to agreement with a company, it can take months for them to actually get it printed and onto the shelves.

So, for example, in the Vioxx situation, having an ability to have a drug watch page where we could have put the information about the clinical trial when it became available would have alerted the public to that well in advance of the labeling change being—the actual details of a labeling change being worked out. It would have been very, very useful.

Senator MURRAY. How long before that drug watch program can be put into place?

Dr. KWEDER. We are in the process of developing processes and procedures for that that will be made available and will seek public comment on those. Our goal is not to blindside the industry on this, which is, of course, a concern. Most of the kinds of things that would be there would be things that they are aware we are working on. These wouldn't be surprises.

Senator MURRAY. Thank you very much. I appreciate your testimony.

Senator BURR. I thank Senator Murray.

The chair would recognize himself. Again, welcome, Dr. Kweder. Let me ask you, can a drug be approved without a clinical trial?

Dr. KWEDER. Well, there may have been some back in the 1920s, but not today.

Senator BURR. Not today.

Dr. KWEDER. Not today.

Senator BURR. So the questions that deal with clinical trials, there are clinical trials that are done on all pharmaceutical products that are approved at the FDA?

Dr. KWEDER. That is correct.

Senator BURR. The COX-2 issue was something that was raised in a study that was looking at other potential indications for COX-2?

Dr. KWEDER. Actually, the first study was looking at a safety—actually looking at a safety issue, but it wasn't heart safety. It was looking at stomach bleeds.

Senator BURR. And that is where we saw the first—

Dr. KWEDER. Correct. Yes.

Senator BURR. Let me ask you from a standpoint of labeling, did the COX-2 drugs refer to any cardiovascular concerns on the original label?

Dr. KWEDER. I am trying to remember. I do believe—no, I don't think so. No, they did not.

Senator BURR. OK. So this was a whole new area?

Dr. KWEDER. It was a whole new area, and actually as we reviewed, particularly Vioxx, as we reviewed that drug, our medical people looked very, very carefully for any evidence of heart problems because of what was known from test tube data about some potential and could not find any.

Senator BURR. Let me go to an area of benefit, if I could, because the statement was made that few patients benefited from COX-2 inhibitors. Do you agree with that statement?

Dr. KWEDER. No, I don't.

Senator BURR. Is there not a population out there that has benefited from this innovative therapy?

Dr. KWEDER. You know, the options to treat pain are not great options, and so anybody who has taken one of these medicines and had relief of their pain, in my estimation, has benefited from the drug.

Senator BURR. My dad is 83 and after this all became public, for 3 weeks, I saw him limp. And when finally I asked why, he said, "Well, I am off my Celebrex." And I said, does anything else work? He said, "No, that was the only thing." And I said, then go back on it. At 83 years old, you have to determine whether the ability to be mobile is in the best interest of your overall health, and today, he doesn't limp because this drug is available to him. Clearly, we want him to make an educated decision based upon all the facts.

Let me ask you about patients in general. Do you find that with the electronic access that patients have that they are informed or uninformed today about not just the capabilities of the drugs, but side effects, as well?

Dr. KWEDER. You know, I actually have the privilege of practicing medicine on a weekly basis and teaching medical students and

residents and I am amazed at how savvy many patients are about their medicines and the risks and benefits of them. I don't think it is enough. I think we need to find additional. Electronics are the number one way that they are finding information on their own and we need to keep that information coming.

Senator BURR. Should we believe today that every patient who has a high cholesterol level in their blood takes a cholesterol-busting drug?

Dr. KWEDER. They don't.

Senator BURR. The likelihood is that there is some piece of information that they read about a drug, that they hear, or ultimately a health care professional identifies a problem, and if they go on that drug, what is the benefit to us?

Dr. KWEDER. The benefit can be substantial. Most of the cholesterol agents have shown—many of the cholesterol agents have shown an improved length of life, decreased mortality.

Senator BURR. As well as overall health care savings to the—

Dr. KWEDER. Absolutely. Unfortunately, some people still aren't getting care for their—taking care of themselves.

Senator BURR. I think it is important to point this out in the context of some of the, at least assumptions that some have led to about direct consumer advertising having no patient benefit. In fact, it does have a patient benefit because in many cases, that is the only way to reach certain individuals.

Let me go to an area that Senator Kennedy was in and that was to ask you to clarify a bit further the proposal on this new safety mechanism or review mechanism at FDA. Clearly, I am one that for the last 7 years has questioned MedWatch, only because it was designed with the primary piece of information coming from physicians. At a period where we were decreasing rapidly the reimbursement of physicians, and the ability to spend time with patients became less and less based upon the reimbursement we enforced, in many cases. I think to believe that doctors would fill out adverse reaction sheets and actually submit them to the FDA, we were dreaming. So I think we have reached the world of reality now with the creation of an entity within FDA to review postapproval pharmaceutical products. But I want to make sure that I clarify the record.

Your inside-outside process, this is an entity within the FDA to look at postapproval review of drugs, to use individuals within the FDA that were not reviewers of that application, and to use outside individuals to come in and be part of your inside review? This is not the creation of an outside entity outside of the FDA, correct?

Dr. KWEDER. Yes, I think that is a good way to characterize it.

Senator BURR. It is using the talents of—

Dr. KWEDER. Using the talents of—right, inside people who have not been involved, and I think that is a really important component is taking people who are at an arm's length from the workings of the data itself, who have perspective, who have some broader perspective.

Senator BURR. How much money do you need to improve drug safety monitoring?

Dr. KWEDER. Well, you know, we have—the President's budget for fiscal year 2006 earmarks \$5 million, an additional \$5 million

for drug safety. That is a good down payment. There are some—I can't give you an exact figure. There have been—this committee has looked at this in the past. I know that there is a letter that was in response to an inquiry of this type from Senator Jeffords—I believe it was in 2000 or 2002, we can get that for you—where there is a much more detailed estimate of, over time, the kind of investment in the system it will take for postmarketing safety and the life cycle of a drug and those assessments to keep pace with the increasing dependence, which is not a bad thing, of our society on medicines to stay healthy.

Senator BURR. Dr. Kweder, I thank you. I don't see any members or Senators who have not asked questions. Hearing none, I would once again like to thank you for your service and thank you for your testimony today.

At this time, I would call up the second panel. Let me introduce those who are on our second panel.

First, Ms. Nancy Davenport-Ennis, CEO of the National Patient Advocate Foundation. Ms. Davenport-Ennis is testifying today in partnership with Friends of Cancer Research. Nancy is a cancer survivor and founding Executive Director of the National Patient Advocate Foundation, a policy organization that seeks to improve access to care through regulatory and policy initiatives at the State and Federal levels. Her testimony will focus on the advances in the drug approval process that have helped speed new therapies to market and how she believes patients have benefited from this.

Dr. Thomas Fleming is a professor in the Department of Statistics and Biostatistics and is Chairman of the Department of Biostatistics at the University of Washington. Dr. Fleming is a member of the FDA's Advisory Committee on Cardiovascular and Renal Drugs and was a member of the joint committee convened to examine the COX-2 arthritis drugs. Dr. Fleming will offer his views on drug safety and risk-benefit analysis.

Dr. David Fassler is a Clinical Associate Professor of Psychiatry at the University of Vermont College of Medicine and Clinical Director of the Otter Creek Associates in Burlington, VT. Dr. Fassler will discuss the FDA's decision to require black box labeling on anti-depressants for children last year and he will bring a clinician's perspective to the impact of that decision.

Dr. Scott Gottlieb is a physician and author of the *Forbes-Gottlieb Medical Technology Investor*. He is a former senior official at the FDA and currently a resident fellow at the American Enterprise Institute here in Washington. Dr. Gottlieb will discuss his ideas for improving drug safety, including using new information tools to improve the process for postmarketing surveillance.

Ms. Abbey Meyers is a founder and President of the National Organization for Rare Disorders, a coalition of national voluntary health agencies and clearinghouse for information about these little-known illnesses. Ms. Meyers is considered the primary consumer advocate responsible for passage of the Orphan Drug Act, the Rare Disease Orphan Products Development Act, and the Rare Disease Act. Ms. Meyers will discuss her perspectives on the FDA drug approval process.

Due to the snowstorm, Ms. Meyers is unable to be here in person, but if you will notice that microphone in the middle of the

table, she is connected technologically through that conference phone and we will have her participate in as much of this as possible. Ms. Meyers, can you hear us?

Ms. MEYERS. [By telephone.] Yes, I can. Thank you.

Senator BURR. Wonderful. I love it when these things work.

Mr. William B. Schultz is a partner in the Washington, DC law firm of Zuckerman Spaeder. Prior to joining Zuckerman Spaeder, Mr. Schultz held the position of Deputy Assistant Attorney General, where he supervised all appellate litigation conducted by the Civil Divisions of the U.S. Department of Justice in the Department's lawsuit against the tobacco industry. Mr. Schultz also served as the FDA's Deputy Commissioner for Policy from 1994 to 1998. Mr. Schultz will discuss his ideas for FDA reform. Bill, it is good to see you again.

At this time, why don't we start at the left. The chair would recognize Ms. Davenport-Ennis for your opening statement.

STATEMENTS OF NANCY DAVENPORT-ENNIS, EXECUTIVE DIRECTOR, NATIONAL PATIENT ADVOCATE FOUNDATION, WASHINGTON, DC; THOMAS R. FLEMING, PROFESSOR AND CHAIR, DEPARTMENT OF BIOSTATISTICS, UNIVERSITY OF WASHINGTON, SEATTLE, WA; DAVID FASSLER, M.D., CLINICAL ASSOCIATE PROFESSOR, DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF VERMONT, COLLEGE OF MEDICINE, AND CLINICAL DIRECTOR, OTTER CREEK ASSOCIATES, BURLINGTON, VT, ON BEHALF OF THE AMERICAN ACADEMY OF CHILD AND THE ADOLESCENT PSYCHIATRY AND AMERICAN PSYCHIATRIC ASSOCIATION; SCOTT GOTTLIEB, M.D., RESIDENT FELLOW, AMERICAN ENTERPRISE INSTITUTE, WASHINGTON, DC; ABBEY S. MEYERS, PRESIDENT, NATIONAL ORGANIZATION FOR RARE DISORDERS, DANBURY, CT; AND WILLIAM B. SCHULTZ, PARTNER, ZUCKERMAN, SPAEDER, LLP, WASHINGTON, DC

Ms. DAVENPORT-ENNIS. Thank you, Chairman Burr. I appreciate the opportunity to be with the committee this morning and I thank you, Senator Murray, for also being here, as well as I would like to acknowledge the Senate staff who is here. Thank you for the opportunity.

I would like to share with you that while, indeed, I am a 14-year cancer survivor, that is probably the least important statement that you will hear me say today. The fact that I am the mother-in-law to a now 29-year-old son-in-law who is a ten-year survivor of nonHodgkin's is far more significant, not to mention the fact that I was the aunt to a now-deceased 34-year-old niece who battled cancer the last 5 years of her life.

I am here to talk to you today on behalf of the 3.2 million Americans who reached out to the Patient Advocate Foundation in the calendar year of 2004 as they were trying to seek access to clinical trials, to newly-approved drugs, and to other areas of health care that were made unavailable to them within the national system.

While the American Cancer Society states to us that one in two men during their lifetime and one in three women during their lifetime will have cancer, I think every one of us in this room have been touched by cancer in one way or another. I am testifying in

partnership today and collaboratively with the Friends of Cancer Research, an organization that raises awareness and provides public information on cancer research.

I am not here to testify as a regulatory nor a statutory authority on how the FDA, indeed, implements its business. I am here to speak with considerable authority on how patients view the role of the FDA in the United States of America.

I do agree that patients concur with Secretary Leavitt as in a speech on February 15 he characterized to the Nation that the FDA is an icon of trust, that they are a certifier of safety, that they are an enabler of innovation, and they are a repository of information. Indeed, I think patients expect the FDA to be all of that.

But patients with cancer are also very reality-focused. They understand that there is no such thing as a drug that is 100 percent safe. They understand that for any drug that they may take, there is also going to be a risk. They understand that in evaluating the risk, they are always looking for the ultimate benefit.

Cancer patients particularly understand the issue of toxicity in newly-approved drugs, and when you are diagnosed with cancer, often, you are making determinations of what are your tradeoffs to take the alkylating agents that are going to kill the disease at the same time that they are killing healthy cells and what do you do to get through that process.

I have to bring you a story of a 27-year-old woman who works with us in the National Patient Advocate Foundation. She lives in Portland, Oregon, and was in nursing school at the age of 22 observing a surgery when she collapsed unconscious on the floor in the surgical suite. It took 6 months to determine that she had an inoperable brain tumor that is malignant. She says to us, in her own words, in a letter written to her doctor when she was 24 years old, the following. "I want to give myself the best shot of surviving as long as I possibly can. I am willing to deal with toxicity."

For cancer patients and for most chronically ill patients, time is the most critical asset that you are looking for in your battle with a life-threatening illness. PDUFA gives us time. PDUFA brings drugs to market more quickly. PDUFA has reduced the standard approval time in 1993 for drugs from 26.9 months to a period of 15.4 months, and if you are fortunate enough to have your drug move into priority review today, that period of time for approval can be reduced to 7.7 months.

For Jarrett Minear, a young man who came to the United States Congress with us last summer, who was diagnosed with cancer with U.N. sarcoma at the age of 2 years old, time was what he was looking for for the 10 years after the diagnosis, for his disease was never stopped. He was never disease-free for one single day for the remaining 10 years of his life. How do we measure the impact of time for a patient like Jarrett Minear, who, due to drug discovery, was able to live for ten additional years after losing his leg at the age of two?

We must maintain the momentum of research. Hundreds of products are in the pipeline now. They promise us less toxicity. They promise us targeted therapies in fields such as genomics and proteomics. Patients view the FDA as the gatekeeper to get the drugs to market safe and effectively.

The FDA has heard the patients. They have created an Oncology Office. They have initiated an FDA-NCI task force. They are moving ahead with the critical path objectives.

I bring to you today what I feel are five pillars of safety reform of FDA. No. 1, patients view safety and efficacy as united and as the foundation of the FDA process of approval.

No. 2, mechanisms to enhance existing structures for post-marketing safety monitoring and adverse event reporting must be explored.

No. 3, efforts to bring greater efficiency and scientific expertise to the agency's review and monitoring processes must continue to empower the agency to keep pace with rapid scientific developments.

The FDA must certainly continue its collaborative work with members of Congress, with other regulatory agencies, with patients, physicians, and the industry to enhance the critical path.

And finally, the FDA must be adequately resourced to implement a comprehensive suite of reforms.

Just as I started my testimony with a quote from Wendy Dixon, I must end my testimony with her words. In the same letter written to her doctor 2 years ago, she said, and I quote, "Words cannot express how much I want to live, and anticipating the loss of my future is devastating. I cannot control cancer. I can control how I choose to fight it."

Let me conclude by saying every member of your committee is to be commended for your thoughtful and deliberative investigation and deliberate decision making in the matter of the FDA's drug approval process. As patients, we welcome the opportunity to work with you collaboratively in that process. And as patients, we know that a robust dialogue in the area of policy and reform will at the end of the day improve access to those drugs that are improving lives of chronically ill patients every day.

Thank you for the opportunity to testify.

The CHAIRMAN. [Presiding.] Thank you very much.

Ms. DAVENPORT-ENNIS. Thank you.

[The prepared statement of Ms. Davenport-Ennis follows:]

PREPARED STATEMENT OF NANCY DAVENPORT-ENNIS

Executive Summary

We welcome the recent discussions about how we can make our drug approval system better, but we are mindful of the fact that patients with life altering diseases like cancer are given hope because of the advances of scientific discovery and development. We support reform that makes drugs safer, but warn against those that might unintentionally slow down the flow of better technology for treatment, prevention, and detection—or worse, discourage their creation altogether. The only way to prevent such unintended consequences is to have a thoughtful policy discussion not about safety alone, but safety in combination with benefit and efficiency. While we of course want safer drugs, we feel that any safety reforms absolutely must be matched with efforts to enhance the FDA's level of efficiency, scientific expertise, and overall capacity to fulfill its numerous mandates.

I. Introduction

Chairman Enzi, Senator Kennedy, and distinguished Members of the Committee, I thank you for the opportunity to discuss the FDA's drug approval process, and its impact on the availability of safe and effective tools for combating devastating diseases like cancer.

My name is Nancy Davenport-Ennis, and I am the CEO of The National Patient Advocate Foundation. We serve as a strong advocate for policy and legislative re-

forms that eliminate barriers to patient access to treatment. Although I am not an expert in the regulatory processes at FDA or the enabling statutes that govern them, I can speak with considerable authority about how patients and survivors view the FDA both today and from a historical standpoint, and what issues like risk, benefit, and timely access mean to those suffering from life altering conditions.

I stand before you as a two-time cancer survivor. Not only have I experienced the burden of this disease first hand, it also has taken the lives of close friends and family members.

I know that many of you on the committee and in the room here today have been touched by cancer as well. According to the American Cancer Society, one out of every two men and one out of every three women will have some type of cancer. An estimated 564,000 people died from cancer in 2004. Cancer has recently surpassed heart disease as the leading cause of death among people under the age of 85.

Although I advocate on behalf of patients with a multitude of life altering diseases, it is against this backdrop of cancer's enormous burden and threat that I would like to offer the committee my thoughts on the FDA's approval process. I would also like to acknowledge that my testimony was developed in partnership with my colleagues at the Friends of Cancer Research—a non-profit organization that raises awareness and provides public education on cancer research in order to accelerate the Nation's progress toward better tools for the prevention, detection, and treatment of cancer.

Both of our organizations take pride in knowing that we work on behalf of patients not only to improve access and quality of care, but also to support a strong national commitment to the research and development necessary to produce innovative medical tools that are both safe and effective.

II. Understanding the Cancer Perspective on Safety and Efficacy

Cancer is a cellular disease that begins in the body long before physical symptoms are usually expressed. Because it is difficult to catch many cancers early (when the disease is often easier to treat and survival rates are typically much higher), many diagnoses come in the later stages of disease where the symptoms are rapidly becoming more acute and the long-term survival prospects are grim. The conventional way of stopping the cancerous cells from spreading is to eradicate them either through surgery, radiation therapy, chemotherapy, or some combination of these options. Many of the cancer drugs used to stop the disease from spreading are unable to discriminate between the cancerous cells and the non-cancerous cells. A great number of healthy cells are consequently destroyed in the treatment process, which can bring uncomfortable and sometimes painfully disabling side effects. Thus, cancer often presents the patient and the physician with the painful tradeoff between burden of treatment and burden of disease.

Cancer patients understand all too well that there is no such thing as a drug that is 100 percent safe. Virtually all approved drugs and biologics have near term side effects and carry some risk. Most agents also pose known and unknown risks associated with chronic use and delayed toxicity. The severity of those side effects and the level of risk will vary from person to person, and from agent to agent. The question is not whether a drug is completely safe or completely effective, but rather how effective is it compared to how safe it is. This risk-benefit balance is the essence of the FDA's review process.

The agency evaluates the risk versus the benefit of a proposed product using a scientifically derived process conducted by experts with the knowledge and judgment necessary to assess the balance between the two. Most importantly, these experts typically have a working knowledge of the condition the product is designed to address so the impact of disease is not overlooked when considering safety and efficacy.

The FDA's review of oncology products differs from its review of other medicinals in that efficacy is often of greater concern than toxicity. While safety is always considered in the review and product label, significant toxicity is generally considered acceptable for oncology drugs given the severe and often fatal nature of the disease being treated.

This approach to the review of oncology products is generally consistent with the manner in which cancer patients and their physicians select from a complex array of treatment options. The safety of a drug or other treatment option is not considered in isolation, but rather the risk of side effects is weighed against the potential benefits a particular course of treatment may provide compared to the risk from spread of disease. The decision about whether or not to deploy powerful and sometimes risky medications in an effort to improve the life of a cancer patient ultimately rests with that particular patient and their prescribing physician.

But because the burden of cancer is usually far more damaging and toxic than the interventions used to stop it, many patients and their caregivers place a premium on the rate at which cancer products are approved and the subsequent access to those products.

As a former cancer patient, I can assure you that time is a very precious commodity to someone diagnosed with cancer. The FDA's capacity to effectively evaluate safety and efficacy is just as critical as the speed at which that evaluation is conducted. When you are suffering from cancer and your expected life span may be months or even weeks, you shouldn't have to wait any longer than is necessary for the FDA to approve new medical products.

It is for that reason that many advocacy organizations across the disease community were so supportive of the Prescription Drug User Fee Act (PDUFA).

III. The Impact of PDUFA

PDUFA initially had 2 primary objectives: (1) reduce the time required for FDA review of new drug and biological product applications, and (2) thereby enable patients to have earlier access to new therapies. Under PDUFA, the FDA collects user fees from industry to supplement annual appropriations for review of new drug applications. According to the Government Accountability Office (GAO), between 1993—when PDUFA was first implemented—and 2001, FDA utilized user fees to increase its medical and scientific drug review personnel by 77 percent. Thanks to the additional resources and staff provided by this legislation and its subsequent versions, the agency has cut nearly in half its 27-month median approval time for standard drugs. This accomplishment means that patients gain access to new drug therapies significantly sooner than they otherwise would.

Based upon an analysis of data available on the FDA's website, the agency approved 953 new drug applications (NDAs) between 1993 and 2003. The average total time for the approval of those applications that underwent "standard review" (745 of the 953) was 26.9 months in 1993 compared to 15.4 months in 2003. The average total time for the approval of those applications that underwent "priority review" (208 of the 953) was 16.3 months in 1993 compared to 7.7 months in 2003. Pursuant to the Food and Drug Administration Modernization Act (FDAMA) of 1997, "priority review" is a designation intended for those products that address unmet medical needs.

For those drugs classified as new molecular entities (NMEs), a term used to describe an active ingredient that has never been marketed in this country, the agency approved 321 applications between 1993 and 2003. The average total time for the approval of those NME applications that underwent "standard review" (192 of the 321) was 27.2 months in 1993 compared to 23.1 months in 2003. The average total time for the approval of NME applications that underwent "priority review" (129 of the 953) was 14.9 months in 1993 compared to 6.7 months in 2003.

Thanks to improvements made in the pace of the FDA's review process over the past decade or so, thousands of cancer patients have had earlier access to new cancer treatments. Consequently, many cancer patients' lives have been extended or their quality of life improved.

For example, according to information found in the FDA's fiscal year 2006 Budget Summary:

"a new biologic for the treatment of breast cancer (Herceptin®/trastuzumab) was approved by FDA in less than 5 months. This drug took 18 months to be approved in Europe. There were an estimated 10,000 American patients with advanced breast cancer who received this new treatment (Herceptin®/trastuzumab) during the time that FDA might have still been reviewing the application, had it not been for the improvements made possible with the additional funds under PDUFA. This added an estimated 2,300 years of life to the population who had access to the new treatment (Herceptin®/trastuzumab) following its market approval in May of 1998."

In making it possible for drugs deemed safe and efficacious to make it to market more quickly, PDUFA has made the difference between life and death for many patients with cancer or other life-threatening illnesses.

IV. We Stand on the Threshold of Incredible Advances in Cancer Research

We are entering an especially exciting time with respect to the development of innovative drug treatments. In recent years, the FDA approved several pharmaceutical products that treat cancer in entirely new ways, such as Avastin® and Erbitux® for treatment of colorectal cancer and Tarceva® for lung cancer.

Incredible progress in fields such as genomics and proteomics has vastly increased our knowledge about cancer's molecular and genetic signals and processes. Such information allows for the detection of cancer at a much earlier stage, when treatment options are often more numerous, less invasive, and more successful. Cancer re-

search also is moving us closer to more targeted treatments, whereby advanced technology can be used to target and destroy cancerous cells without damaging the body's healthy cells. Finally, the scientific foundation has been laid for the technological capacity to prevent cancer growth altogether by blocking or interfering with the molecular signals that turn healthy cells into cancerous cells.

We look to the National Institute's of Health, our Nation's many academic research institutions and community oncology practices, in addition to pharmaceutical and biotech firms to invest an enormous level of resources into Research and Development in order to develop better tools for preventing disease, detecting it sooner, and treating it more effectively.

We then look to the FDA to serve as a gatekeeper for the entry of those products into the market so that patients have access to those deemed "safe and effective." Once those products are approved, we rely upon the agency to provide sufficient information about a product's risks and benefits so that patients and their caregivers are empowered to make personalized decisions about their care.

With literally hundreds of oncology products now in the developmental pipeline, the demand upon FDA for advice and review will rapidly accelerate. Thus, the agency's regulatory oversight of cancer research must be as rationally and efficiently structured as possible in order to insure timely delivery of cutting edge science to patients.

The FDA took a positive step in the right direction last July when it announced the formation of an Oncology Office that would allow for better consolidation and integration of the Agency's cancer-specific expertise. The Interagency Oncology Task Force formed between FDA and the National Cancer Institute in 2003 also has been a positive step toward enhancing the efficiency of clinical research and the scientific evaluation of new cancer medications. Through this program, Federal researchers and regulators have been developing ways to share knowledge and resources that will accelerate the development of new cancer drugs that are safe and effective.

However, we are deeply concerned that potential efforts to legislate unrealistically heightened degrees of certainty with respect to the safety of drugs could turn back the clock on what we view as important reforms in terms of improved efficiency and accelerated access to vital drug therapies achieved by the FDA. Our patients simply cannot afford unduly burdensome regulatory or bureaucratic requirements that could halt such progress or unravel the gains made since enactment of PDUFA.

V. Be Cautious With Safety

We appreciate the committee's scrutiny of recent concerns regarding drug safety, and we share your commitment to assuring that information about risks associated with drugs is identified and disseminated as early as practicable. However, it is important to always keep in mind that beneficial drug products are going to have associated with them a certain amount of risk. Aspirin has risks; penicillin has risks; the vaccines we give our babies to immunize from disease like polio and diphtheria carry risk. No drug is ever 100 percent safe.

Just like patients and their caregivers must weigh the benefits and risks associated with a particular product when deciding whether or not to use it to fight or prevent disease, we feel that the FDA must continue to carefully weigh the benefits and risks associated with a product when deciding whether or not to grant approval. For that reason, we would advise against any effort that creates new regulations or bureaucracy that isolates or further separates either the drug safety function or the drug efficacy function from the overall drug review process. Safety and efficacy must never be viewed in isolation from each other. The FDA's review process should remain structured in a way that emphasizes the benefit-risk balance of a medicine as a basis for approval.

Drug reviews that are not based on this delicate balance will almost certainly discourage research on new therapies for dread diseases like cancer and AIDS. It may become very difficult to get a drug approved for cancer treatment if the regulatory hurdles for safety are too high because those drugs are likely to have some level of side effects, and they are likely to be used in a patient population that is sick and vulnerable to adverse reactions.

Of even greater concern is how an overemphasis on safety might have a devastating impact on the advancements being made in our ability to detect cancer early or prevent it altogether. Remember, cancer is a biological process that starts in the body years or even decades before a diagnosis is made. The ability to detect that process early or stop it all together represent our greatest hope for significantly reducing or eliminating the suffering and death due to cancer. The conundrum is that the clinical testing and medical application of new technologies for early detection and prevention will involve people at risk for cancer who are not yet showing signs of advanced disease and may be entirely without symptoms. However, the tools for

early detection and prevention are going to have side effects, just like any medical intervention. If the regulatory hurdles for safety are too high, it will be very difficult to get new tools for prevention and early detection approved even though they may save hundreds of thousands, if not millions, of lives in the not too distant future.

And who is going to pour billions of dollars into the research and development of new cancer products if they are not likely to be approved because they might not be considered safe enough irregardless of their benefits, or if they will face an even longer and less efficient review process?

VI. What we support

Of course the FDA's role in evaluating and monitoring safety should be strengthened. But more importantly, we want safer and more effective drugs moved through the system as efficiently as possible so they can be used as soon as possible by those who need them most, such as cancer patients and/or those at high risk for cancer.

We would prefer strategies and solutions designed to improve the FDA's capacity in the areas of safety, efficacy, and efficiency simultaneously. At the very least, any effort to improve one aspect of these factors alone should not be implemented without careful consideration of how the other two might be impacted. And this means that FDA's budget must be considered accordingly.

The following are the 5 key "Pillars of Safety" that we think are critical to reforms at the FDA:

1. Safety and Efficacy must continue to be the foundational elements of the FDA regulatory process. Safety cannot exist in a vacuum apart from efficacy.
2. Mechanisms to enhance existing structures and processes for post market safety monitoring and adverse event reporting must be explored.
3. Efforts to bring even greater efficiency and scientific expertise to the FDA's review and monitoring processes must continue; such efforts must be done in a manner that empowers the Agency to keep pace with the rapid advancements now occurring in areas such as genomics, proteomics, and nanotechnology.
4. FDA must continue to work with industry, patient groups, physicians, hospitals, academia, and other government agencies to enhance the critical path.
5. The FDA must be sufficiently resourced in order to insure more effective pursuit of its existing mandates. Additional resources are even more essential if FDA is to successfully implement a comprehensive suite of reforms.

We are encouraged by FDA's plan to allocate more than \$70 million over 5 years to support enhanced monitoring and surveillance of risks that may be associated with drug products already on the market. However, no drug is without risk; and it always has been an unfortunate but unavoidable fact that some adverse effects may not become apparent until after a drug has been in wide or extended use. We can hope to minimize such adverse effects and enhance the agency's capacity to report them, but we must also accept certain risks associated with beneficial drug products. Moreover, without new monies, every dollar the FDA shifts towards new regulations and infrastructure for safety is money taken away from programs that allow the agency to more effectively and efficiently evaluate risk and benefit together.

Finally, one of the keys to a stronger FDA and a more robust development pipeline is a clear plan for how the agency will work to modernize the medical product development process. We are pleased that such a proposal has been presented in the recently published report: "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." This document details the agency's plan to update the tools currently used to assess the safety and efficacy of new medical products. We fully support the FDA's willingness to reach out to numerous stakeholders in an effort "to coordinate, develop, and/or disseminate solutions to scientific hurdles that are impairing the efficiency of product development industry-wide."

V. In Conclusion

We welcome the recent discussions about how we can make our drug approval system better, but we are mindful of the fact that patients with life altering diseases like cancer are given hope because of the advances of scientific discovery and development. We support reform that makes drugs safer, but warn against those that might unintentionally slow down the flow of better technology for treatment, prevention, and detection—or worse, discourage their creation altogether. The only way to prevent such unintended consequences is to have a thoughtful policy discussion not about safety alone, but safety in combination with benefit and efficiency. While we of course want safer drugs, we feel that any safety reforms absolutely must be matched with efforts to enhance the FDA's level of efficiency, scientific expertise, and overall capacity to fulfill its numerous mandates.

The CHAIRMAN. Dr. Thomas Fleming?

Mr. FLEMING. Senator Burr, Senator Enzi, thank you for the invitation to discuss what Congress and the FDA need to do to both protect and promote public health with respect to drugs and biologics.

The regulatory approval of drugs and biologics for marketing in new clinical indications should be based on evidence from adequate and well-controlled trials that reliably establish that the product has a favorable benefit-to-risk profile. Therefore, these clinical trials must give robust and compelling evidence that the product provides clinically and statistically significant beneficial effects on outcomes that unequivocally reflect tangible benefit to patients, such as relieving disease-related symptoms, improving the ability to carry out normal activities, and in life-threatening disease settings, prolonging survival.

In turn, sufficient safety data should be obtained to provide reliable evidence that these beneficial effects outweigh safety risks to patients who will use these products in a real world setting. It follows that the level of safety risks that would be judged to be acceptable would depend on the level of benefit provided by the intervention.

Multiple sources of information are useful in monitoring these safety signals, including pre-marketing evaluations, usually from randomized control trials, but safety monitoring in a postmarketing setting is also extremely important and has many components, including postmarketing passive surveillance, usually through voluntary submission of AEs thought by caregivers to be related to treatment, and more informative and reliable postmarketing active surveillance, such as that provided by large-link databases, and particularly for products that will have widespread use.

This source was very informative in assessing safety of COX-2 inhibitors. Even more informative for the COX-2s were postmarketing randomized trials to determine if one can rule out unacceptable increases in the rate of clinically significant safety risks that are uncommon or occur on a delayed basis when evidence has been obtained to suggest the plausibility of such risks.

In evaluating the effects of COX-2 inhibitors on the risk of cardiovascular mortality, MI, and stroke, the FDA proceeded in a proper manner regarding the accumulation of data from both observational studies and randomized trials and regarding the development of benefit-to-risk assessments for this class of agents using these data.

Even though the FDA process for drug review is one of the best in the world, in fact, I think the best in the world, some modifications would enable needed improvements. I have outlined, proposed, a number of potential improvements or approaches in my written testimony.

Among these, when a safety signal is found, I believe FDA should have greater authority to require control trials, usually randomized trials, that will have the ability to determine whether unacceptable safety risks truly exist.

Another point, another recommendation, the accelerated approval Subpart (h) regulatory process was established to allow marketing of products that have been shown to have compelling effects

on biomarkers, for example, shrinking tumors, if these effects are, quote, "reasonably likely to predict clinical benefit," unquote, and if the sponsor completes in a timely manner one or more trials that will validate that the intervention truly does provide meaningful beneficial effects on true clinical efficacy outcome measures, such as relieving disease-related symptoms or prolonging survival.

Unfortunately, many challenging issues arise from the implementation of the accelerated approval process that can lead to compromising what is truly in the best interest of public health, which is the reliable as well as timely evaluation of interventions' safety and efficacy. Congress and the FDA should consider policies to reduce the likelihood that products are used for a lengthy interval of time by patients in nonresearch settings, even though the efficacy has not been established, and even though available safety data are much more limited than what would typically be available from completed trials evaluating effects on clinical efficacy outcome measures.

In closing, it should be noted that one change that should not be made is the creation of a separate group outside FDA to review safety and efficacy. First, regulatory experts at FDA have particular experience and familiarity with the drug approval process, including the Code of Federal Regulations, and the limits of the authority of the FDA.

Second, it is unclear how recommendations of such an outside organization would be incorporated into the functioning of the FDA.

Finally, there are significant conflict of interest issues for many outside FDA who might be selected to serve in a separate safety group.

The FDA is not broken. The process of drug review works very well. In general, the FDA has been very effective in carrying out its regulatory responsibilities, and in turn, has had a profoundly favorable influence on the process of promoting and protecting public health. Thank you.

The CHAIRMAN. Thank you.

[The prepared statement of Mr. Fleming follows:]

PREPARED STATEMENT OF THOMAS R. FLEMING, PH.D.

Thank you for the invitation "to provide my professional opinion on what, if anything, Congress and the FDA need to do both to protect and to promote the public health with respect to drugs and biologics, including a discussion about what changes might need to be made to ensure that FDA is fully considering both benefits and risks during pre- and post-market review". My testimony is based on 28 years experience in collaborating on the design, conduct and analysis of government and industry sponsored clinical trials, and on nearly 20 years service on FDA Advisory Committees.

EXECUTIVE SUMMARY

- A. Decisions regarding marketing of drugs and biologics should be based on robust and compelling evidence that the intervention has a favorable benefit-to-risk profile.
- B. In general, the FDA has been very effective in carrying out its regulatory responsibilities and, in turn, has had a profoundly favorable influence on the process of promoting and protecting public health.
- C. In evaluating effects of Cox-2 inhibitors on the risk of cardiovascular mortality, MI and stroke, the FDA proceeded in a proper manner regarding the accumulation of data from observational studies and randomized trials and regarding the development of benefit-to-risk assessments for this class of agents using these data.
- D. The FDA should retain the responsibility for evaluation of safety of drugs and biologics.

E. Multiple sources of information are useful in monitoring for safety signals, including (i) pre-marketing evaluations (usually from randomized controlled trials) that are of sufficient size and duration to provide robust and compelling evidence that the product has a favorable benefit to risk profile; (ii) post-marketing passive surveillance, such as is provided by the Adverse Event Reporting System (AERS); (iii) post-marketing active surveillance, such as is provided by large linked data bases, in particular for products that will have wide spread use; and (iv) post-marketing randomized trials to rule out unacceptable increases in the rate of clinically significant safety risks that are uncommon or occur on a delayed basis, when evidence has been obtained to suggest the plausibility of such risks.

F. Some modifications that would need to be effected by legislation would enhance the effectiveness of the FDA. These include: (i) providing increased funding to FDA to support scientific pursuits and improve regulatory effectiveness of reviewers; (ii) encouraging FDA reviewers to communicate more effectively with the public; (iii) when safety risks are found, requiring controlled studies (usually randomized trials) that have the ability to determine whether an unacceptable safety risk truly exists be conducted in a timely manner; (iv) improving methodology for safety monitoring in children; (v) establishing a funding program at FDA for observational studies and clinical trials; and (vi) for agents that have received Accelerated Approval under subpart H, ensuring the FDA has policies in place regarding timeliness of completion of validation trials and prompt withdrawal of the product from the market if the validation trials fail to provide robust and compelling evidence that the product has a favorable benefit-to-risk profile.

INTRODUCTION

The regulatory approval of drugs and biologics for marketing in new clinical indications should be based on evidence from adequate and well controlled clinical trials that reliably establish that the product has a favorable benefit-to-risk profile. Therefore, these clinical trials must give robust and compelling evidence that the product provides clinically and statistically significant beneficial effects on clinical efficacy outcomes that unequivocally reflect tangible benefit to patients. Examples of such beneficial effects would be relieving disease related symptoms, improving the ability to carry out normal activities, or reducing hospitalization time while, in the setting of life threatening diseases, the most important beneficial effect often would be prolonging survival. In turn, sufficient safety data should be obtained to provide reliable evidence that these beneficial effects outweigh the safety risks to patients who will use these products in a real world setting. It follows that the level of safety risks that would be judged to be "acceptable" would depend on the level of benefit provided by the intervention.

While sponsors from industry and sponsors from government agencies other than FDA regularly make valuable contributions to the development of greatly needed interventions for treatment and prevention of disease, the reality is that important financial and professional conflicts of interest can result in advocacy for marketing products that have not been established reliably to be safe and effective, placing the public at significant risk. In general, the FDA has been very effective in carrying out its responsibilities to regulate the activities of these sponsors, to ensure that products that are being marketed truly do have a favorable benefit-to-risk profile. Through this achievement, the Agency has had a profoundly favorable influence on the process of promoting and protecting public health.

Before discussing potential refinements to the FDA drug approval process, some aspects of the current process for evaluating safety and efficacy should be reviewed.

EVALUATING SAFETY: SOME BACKGROUND REGARDING AVAILABLE APPROACHES

The review of safety of new products is a complex and multidimensional undertaking. The FDA considers reports of adverse drug reactions from available clinical data, pursues concerns raised by animal toxicology, pursues insights from pharmacokinetic and pharmacodynamic assessments including potential risks of drug-drug interactions, looks specifically for class effects, and searches for rare events. This effort is guided by their wealth of experience. For example, before approval, lack of adverse effects on patient survival must be established for most new drugs for heart failure (due to the experience with inotropes) and for antiarrhythmics (due to the experience with encainide and flecainide).

There are several clinical data sources providing insights about safety risks of new products. In the pre-marketing setting, the most reliable of these sources is the randomized controlled trial. Pre-marketing clinical trials should be of sufficient size and duration to provide robust and compelling evidence that the product has a favorable benefit to risk profile. When evaluating products (such as analgesics, anti-

histamines, antidepressants, and asthma remedies) not expected to reduce mortality or to prevent irreversible morbidity (such as reducing the risk of stroke, permanent loss of vision, or HIV infection), one might need evidence from randomized trials that cumulatively involve more than 10,000 patients. This is particularly important when available evidence suggests plausibility of clinically significant safety risks. The evaluation of Cox-2 inhibitor pain relievers provides an illustration. Given that products in this class provide only a limited reduction in risk of significant upper GI ulcers and have not been established to provide improved pain relief relative to non-specific NSAIDS such as naproxen, new members of the Cox-2 inhibitor class should not be approved until evidence is available from randomized trials ruling out the possibility that that these new agents induce a 50 percent relative increase in the risk of major cardiovascular (CV) events, including CV deaths, MIs and stroke, (i.e., ruling out that the drug causes at least 5 additional major CV events per 1000 patients treated, in a population having a background rate of such events of 1 percent).

Once the product is approved, it is important to continue monitoring for safety signals. Post-marketing passive surveillance, such as is provided by the Adverse Event Reporting System (AERS), is useful for detecting large increases in clinically important rare events, such as establishing the risk of intussusception with a rotavirus vaccine, or assessing the risk of encephalopathy with the acellular pertussis vaccines, or detecting the risk of Stevens-Johnson rash in the treatment of patients infected with HIV. The Office of Drug Safety is responsible for monitoring AERS. However, this system has significant limitations. It is based on voluntary submission of MedWatch forms for adverse events that caregivers believe might be drug related. Underreporting, the lack of denominators and the lack of comparator groups make such information very difficult to interpret in many settings. These types of irregularities in safety information have led to considerable difficulties in the assessment of the relationship of the class of Selective Serotonin Reuptake Inhibitor (SSRI) agents regarding the risk of suicidal ideation and/or attempts.

Post-marketing active surveillance, such as is provided by large linked data bases (the Northern California Kaiser data base being a classic example), provides an improvement over passive surveillance, through more systematic collection of adverse events, yielding complete numerators (i.e., safety events) and denominators (i.e., people exposed to the product). This enhanced approach to post-marketing safety assessment should be more widely implemented for products that will have widespread use. This type of evidence could significantly enhance the insights into whether there is a true causal relationship between SSRI agents and the risk of suicidal ideation and/or attempts. However, this approach also has important limitations. Due to lack of a randomized control group, frequently unavailable confounder information (such as aspirin use or smoking history when studying Cox-2 inhibitors), concerns regarding outcome specificity (are reported events truly events?) and sensitivity (are true events reliably captured?) partly due to recall bias, and concerns resulting from loss to follow-up and the lack of a proper "time 0" cohort, results from these analyses can be very misleading, especially when one is attempting to determine whether an intervention induces a clinically important safety risk that corresponds to less than a 2-fold increase in rate of occurrence of these safety events. These concerns appear to be relevant to the setting of Cox-2 inhibitors. While their effect on the risk of CV deaths, MI and stroke is clinically significant, it appears that this effect is approximately at the level of a 1.5 fold increase. In such settings, the FDA properly would view such "epidemiological" or "observational" evidence to be hypothesis generating or clues regarding safety signals. The FDA properly recognized that it was necessary to conduct post-marketing randomized trials, with large sample sizes and long term follow-up, to reliably address the CV safety risk of the Cox-2 inhibitor class.

When an important safety signal has been suggested but has not clearly been established by active and passive surveillance, post-marketing randomized trials should be conducted to rule out unacceptable increases in the rate of clinically significant safety risks that are uncommon or occur on a delayed basis. The aggregation of evidence from such large scale randomized trials, conducted in pre- and post-marketing settings, has served as the most reliable source of information to the address class effect of Cox-2 inhibitors regarding risk of CV death, MI and stroke. In order to have high reliability in detecting a tripling in the rate of a serious safety event that would occur at the rate of 1 per 1000 patients, the post-marketing randomized trial would need to have approximately 20,000 patients. Several examples exist, in addition to the Cox-2 setting, where trials of this type have been conducted. Two such examples are the evaluation of the cardiovascular mortality risks of anti-psychotics known to induce increases in QTc, and the assessment of the risk of respiratory-related deaths and respiratory-related life-threatening experiences in pa-

tients currently receiving prescription asthma medications. Large post-marketing clinical trials have frequently provided insights about safety risks that were inconsistent with prior expectations based on observational studies or effects on biomarkers (i.e., surrogate endpoints). For example, the ALLHAT trial established that a calcium channel blocker did not have adverse effects on cancer risk, MI or death, and the Women's Health Initiative showed that observational studies improperly characterized the effects of hormone use in women on cardiovascular risk. In a stunning example, even though encainide and flecainide had been shown to suppress arrhythmias, a known risk factor for sudden death (resulting in off-label use annually by hundreds of thousands of Americans), the 2000 patient CAST trial established that these antiarrhythmic agents actually tripled the death rate. Even though the overall death rate was tripled by these agents, this excess risk was not recognized until the availability of the results of the randomized trial.

EVALUATING EFFICACY

As discussed earlier, drug safety cannot be considered separately from drug efficacy/effectiveness since they are both part of an overall assessment of benefit-to-risk. This was recognized in 1962 when the Food Drugs and Cosmetic Act was amended to include that drugs should demonstrate substantial evidence of efficacy as well as safety.

A rich science exists regarding design, conduct and analysis issues that are influential in the achievement of robust and compelling evidence that a product provides clinically and statistically significant beneficial effects. These issues therefore have major regulatory importance, and draw a great deal of attention from both clinical and statistical reviewers at the Agency. Some of these that frequently are most critical in the interpretation of efficacy data are: (i) factors that influence bias and variability, including the role of randomization, the influence of loss to follow up, the need to conduct intention to treat analyses, and the role of blinding; (ii) choosing proper endpoints, and the role of biomarkers as surrogate endpoints; (iii) avoiding biocreep when conducting non-inferiority analyses to establish efficacy of new products when being compared to standard of care interventions; (iv) the role of subgroup analyses; and (v) procedures for monitoring registrational trials to address ethical and scientific concerns.

The second issue in the previous paragraph deserves particular attention. It is often proposed that regulatory assessments of efficacy be based on evaluation of effects on biomarkers, such as transient tumor shrinkage in oncology, or suppression of arrhythmia in cardiology, or decolonization for antimicrobials, rather than evaluating effects on clinical efficacy outcomes that unequivocally reflect tangible benefit to patients, such as duration of survival, disease-related symptoms, or ability to carry out normal activities. The use of biomarkers as replacement or "surrogate" endpoints for the clinical efficacy outcomes enables trials to be conducted with smaller numbers of patients and in shorter periods of time. Regrettably, these surrogate endpoint trials often give misleading results about whether the product truly provides beneficial efficacy, as illustrated earlier by the fact that encainide and flecainide suppress arrhythmias and yet have an adverse effect on mortality.

The Accelerated Approval (AA) (subpart H) regulatory process was established to allow marketing of products that have been shown to have compelling effects on biomarkers, if these effects are "reasonably likely to predict clinical benefit", and if the sponsor completes, in a timely manner, one or more trials that will validate that the intervention truly does provide meaningful beneficial effects on true clinical efficacy outcomes. Unfortunately, as discussed in the accompanying publication (Fleming TR, "Surrogate Endpoints and FDA's Accelerated Approval Process: The challenges are greater than they seem", *Health Affairs* 24: 67-78, 2005), many challenging issues arise from the implementation of the AA process that can lead to compromising what is truly in the best interest of public health: the reliable as well as timely evaluation of an intervention's safety and efficacy. This publication discusses policies that Congress and the FDA should consider to reduce the likelihood that products are used for a lengthy interval of time by patients in non-research settings, even though efficacy has not been established and available safety data are much more limited than what would typically be available from completed trials evaluating effects on clinical efficacy outcomes.

POTENTIAL REFINEMENTS TO THE FDA DRUG APPROVAL PROCESS

The FDA is not "broken". The process of drug review works very well. In general, the FDA has been very effective in carrying out its regulatory responsibilities and, in turn, has had a profoundly favorable influence on the process of promoting and protecting public health. Leaders at FDA such as Robert Temple, M.D., (Director,

Office of Medical Policy; Director, Office of Drug Evaluation I), are extremely knowledgeable, fair, and highly effective in guiding the FDA in the achievement of its mission. Such people are national treasures.

Even though the FDA process for drug review is one of the best in the world, some modifications that would need to be effected by legislation would enable important improvements. Before discussing these, it should be noted that one change that should not be made is the creation of a separate group, outside FDA, to review safety or efficacy. First, the regulatory experts at FDA have particular experience and familiarity with the drug approval process including the Code of Federal Regulations and the limits of the authority of the FDA. Second, it is unclear how the recommendations of such an outside organization would be incorporated into the functioning of the FDA. Finally, there are significant conflicts of interest issues for many outside FDA who might be selected to serve in a separate safety group.

The following are potential changes regarding FDA that should be considered:

1. Increase funding to FDA to allow more person power to accomplish necessary tasks, while allowing reviewers time for scientific pursuits that will improve their regulatory effectiveness. Increased funding would also allow better research within FDA on clinical trials methodology.

2. FDA reviewers should have better communication with the public. Reviewers should be encouraged to publish important points or summaries of their reviews in peer reviewed publications in order to better inform the public regarding efficacy and safety of drugs. (Many scientific articles published by the academic and industry scientists have a "sponsor spin", resulting in reduced objectivity and biased presentation of evidence regarding the benefit to risk profile of the product.)

3. When a safety signal is found, frequently from non-controlled post-marketing data, FDA should require that controlled studies (usually randomized trials) that have the ability to determine whether an unacceptable safety risk truly exists, be conducted. When such trials are conducted in post-marketing settings, requirements for timely completion should be in place.

4. Safety monitoring in children needs better methodology. Currently, the ability to assess rare or long term safety risks, such as for SSRIs, too often is inadequate. Furthermore, when it is unclear how to measure an adverse event in a child, the sponsor should be required to develop methodology to study the safety event in order to be allowed to pursue an indication if the disease is not serious or life threatening.

5. An FDA funding program for observational studies and clinical trials should be established. Among the uses for these funds would be (i) enabling the FDA to have access to evidence from large linked data bases, allowing timely detections of safety signals once products are marketed, in particular for products that will be widely used in settings where rare or long term safety risks could lead to an unfavorable benefit-to-risk profile; (ii) enabling the conduct of important placebo controlled efficacy and safety trials as well as those with generic drugs that will not be conducted by industry or NIH; and (iii) providing funding to develop better tools for clinical trials in the Critical Path program headed by Dr. Janet Woodcock.

6. For interventions that are allowed to be marketed under (subpart H) accelerated approval, the FDA should have policies requiring that clinical trials are in place at the time of the accelerated approval that can reasonably be expected to provide statistically compelling evidence, within a well-defined rapid time frame, about whether the intervention as a favorable benefit-to-risk profile by being safe and by providing clinically meaningful tangible benefit to patients; and the product will be withdrawn from the market promptly if the validation trial does not conclusively provide this required positive evidence.

The CHAIRMAN. Dr. David Fassler, please.

Dr. FASSLER. Thank you. My name is David Fassler. I am a child and adolescent psychiatrist practicing in Burlington, VT. I am also a Clinical Associate Professor in the Department of Psychiatry at the University of Vermont. I am speaking today on behalf of the American Psychiatric Association, where I serve on the Board of Trustees, as well as the American Academy of Child and Adolescent Psychiatry, where I serve as Vice-Chair of the Assembly. These organizations would like to thank Senator Enzi for holding this hearing.

I would like to address four main issues. First, I would like to emphasize the importance of open access to data from clinical

trials, including data from negative trials and unpublished research. Already this morning, you have heard a lot about the issue of clinical trials.

In February of last year, when I testified before the FDA Advisory Committee, there were only four controlled studies in the published literature on the use of SSRI anti-depressants in the treatment of childhood and adolescent depression. However, as we learned in preparation for the hearing, there were actually another 11 unpublished studies whose results had been submitted to the FDA but really weren't known to most practicing physicians.

Physicians and parents clearly need access to this kind of information in order to make fully informed decisions about treatment options. For this reason, the APA and the Academy have been in the forefront of the call for the development of a publicly accessible national registry of clinical trials.

Next, let me try and talk about medication in general and the SSRI anti-depressants in particular. Research has clearly demonstrated that medication can be helpful and even life-saving for many children and adolescents with psychiatric disorders, but medication is most effective when it is used as a component of a comprehensive treatment plan individualized to the needs of the child and family.

Let me take a minute to try and address the complex issue of whether or not the SSRIs increase the risk of suicidal thinking or behavior. At this point, here is what we actually know from a scientific perspective. Contrary to frequent reports in the popular media, there is no evidence to suggest that these medications increase the risk of suicide in children and adolescents. It does appear that these medications may increase the likelihood that a patient, whether it is a child, an adolescent, or an adult, will actually tell someone about their suicidal thoughts or even about a suicide attempt. From my perspective as a psychiatrist, this is actually a good thing because it means you have the opportunity to intervene and to keep the person safe.

I believe this is why none of the studies have demonstrated any increase in actual deaths from suicide in conjunction with the use of these medications. On the contrary and fortunately, the adolescent suicide rate in the country has actually declined by over 25 percent since the early 1990s in a manner consistent with the increased use of SSRI anti-depressants.

Let me underscore the importance of ongoing research in this area. There is no question that we need more information on how to best use these medications in the treatment of our child and adolescent patients. In particular, we need long-term follow-up studies on both safety and efficacy. Fortunately, several such studies are currently underway with funding from the National Institutes of Mental Health.

The APA and the Academy also support the formation of a Pediatric and Adolescent Central Nervous System Advisory Committee at the FDA comprised of experts, including child and adolescent psychiatrists and pediatric neurologists. We also need to address the overall shortage of pediatric mental health specialists, both in research and in clinical practice, and we appreciate the efforts of Senators Bingaman and Collins on this important issue.

Finally, let me emphasize the importance of advocacy for children and adolescents with psychiatric disorders. Parents, in particular, need to be advocates for their children. They need to make sure their kids have a comprehensive evaluation by a trained and qualified mental health professional and that they have access to the necessary and appropriate ongoing treatment services. They should also ask lots of questions about any proposed diagnosis or treatment plan.

To this end, the APA and the Academy have jointly developed a new website, www.parentsmedguide.org, to provide parents and physicians with as much information as possible about the evaluation and treatment of childhood and adolescent depression. Over a dozen major medical family and patient advocacy organizations have already endorsed this effort, and Senator Burr earlier was talking about the importance of electronic access to information and that is exactly why we have set this up in this manner.

We at the APA and the Academy are hopeful that today's hearing and testimony will help promote access to information, encourage expanded support for research, and enhance the ability of parents to advocate effectively for the treatment their children need and deserve.

Thank you for the opportunity to appear before you today.

The CHAIRMAN. Thank you.

[The prepared statement of Dr. Fassler follows:]

PREPARED STATEMENT OF DAVID FASSLER, M.D.

Introduction

My name is David Fassler. I am a child and adolescent psychiatrist practicing in Burlington, Vermont and a Clinical Associate Professor of Psychiatry at the University of Vermont. On behalf of the American Academy of Child and Adolescent Psychiatry (AACAP) and the American Psychiatric Association (APA), I appreciate the opportunity to submit this testimony regarding the Food and Drug Administration (FDA) approval process.

The AACAP is a medical membership association established by child and adolescent psychiatrists in 1953. With over 7,000 members, the AACAP is the leading national medical association dedicated to treating and improving the quality of life for the estimated 7–12 million American youth under 18 years of age who are affected by emotional, behavioral, developmental and mental disorders. The AACAP supports research, continuing medical education and access to quality care. Child and adolescent psychiatrists are the medical specialists trained in the treatment of mental illnesses in children and adolescents.

APA is the Nation's oldest medical specialty society, founded in 1844, with over 35,000 members nationwide specializing in the diagnosis, treatment and prevention of mental illnesses including substance abuse disorders.

The AACAP and APA would like to thank Senator Enzi (R-WY), chair of the Health, Education, Labor, and Pensions Committee, for holding this hearing and for his interest in the Food and Drug Administration's (FDA) approval process and its impact on pediatric medications used to treat depression.

The FDA's drug approval process is basically sound. However, based on our recent experience with the review of the safety and efficacy of the selective serotonin re-uptake inhibitor (SSRI) antidepressants, we believe the process can be further strengthened by implementing four recommendations. First, enhanced reporting of and access to data from clinical trials, including negative trials and unpublished results, in a centralized, publicly accessible registry. Second, an expanded emphasis on post-marketing surveillance and increased funding for long term follow up. Third, the creation of an FDA advisory board focusing on the child and adolescent central nervous system, and fourth, strengthening the workforce of researchers, including experts in pediatric psychiatry and neurology, who can assist with the design, oversight, interpretation and reporting of clinical research.

1. APA and AACAP Urge Access to Comprehensive Clinical Trial Data

The FDA's mission is to advance public health by helping speed innovations that make medications more effective, safer and more affordable; and to provide physicians and the public with the accurate, science-based information they need to use medications to improve their health. That mission depends on open access to all relevant information from clinical studies, especially those that involve children.

The recent discussion of SSRIs brought to light the fact that the physicians, researchers and the public often do not have access to such full data sets. For example, of the 15 studies on the use of SSRIs in the treatment of childhood and adolescent depression, only four had been published as of February 2004.

Research is key to understanding the cause of depression, especially in children and adolescents, and access to both negative and positive research findings is essential to help clinicians develop the most effective treatment plans. It is this principle that led the AACAP and the APA, last summer, to urge the American Medical Association, to join their call for the development of a national registry of clinical trials. While the AACAP and the APA are primarily concerned with psychiatric medications, we recognize that a registry will impact all of medicine. Moreover, we also recognize that there is a bias toward the publication of positive research findings, which affects all areas of health care. Physicians and patients must have all available knowledge about a medication's safety and effectiveness before they can make informed decisions about treatment options.

The AACAP and the APA encourage the FDA to provide broader dissemination of information gained from pediatric clinical trials. Label information and package inserts provide critical information to physicians, but we would urge the agency to routinely include any and all data specifically addressing the safety and efficacy of agents when used in the treatment of pediatric patients.

Our organizations want the public and physicians to get the most accurate and up-to-date information about SSRIs and about all psychotropic medication for children and adolescents. For this reason, the AACAP and APA have recently released two guides on the use of medication in treating childhood and adolescent depression—one for patients and families and one for physicians. Both documents were endorsed by numerous medical, family, and patient advocacy organizations. A new web site was launched (www.ParentsMedGuide.org) to share these documents with the public. Material from the website is appended to this testimony. The parents guide provides advice for parents to help them make the best decision for their child or adolescent with depression. It describes what a black box warning means, what prompted the warning on SSRIs, what treatments are most effective in treating depression, and the risks associated with not treating this condition. The physician's guide, while similar to the parent's guide, includes more specific clinical and research data on diagnosis, treatment efficacy, and suicidality in children and adolescents.

a. Prevalence of Depression in Children and Adolescents

Mental and behavioral disorders affect an estimated 20 percent of children and adolescents, or approximately 10 million young people. Tragically, only one in five receive any form of treatment for these disorders (U.S. Surgeon General Report).

Within this total, clinical depression is a frequently occurring disorder. It is estimated that depression affects 2.5 percent of children and over 8 percent of U.S. adolescents. These rates account for approximately 2.6 million youth ages 6–17 (Birmaher et al.).

Depression and related mood disorders are serious illnesses for most children and adolescents diagnosed with the condition. Depression can interrupt a youth's normal emotional development, negatively affect self-esteem, interfere with learning in school, and undermine friendships with peers. Over 500,000 adolescents attempt suicide each year and depression is most often the cause (Kochanek, KD et al.).

No single cause of depression has been identified. However, we know that depression is an illness with a pronounced biological basis. Research has clearly demonstrated that depression is associated with deficiencies in specific brain chemicals such as serotonin and norepinephrine. The genes that a child inherits also predispose a person to the illness, but this predisposition, or vulnerability, to depression typically is "triggered" by life events. Researchers have begun to identify these triggers, called *risk factors*, for depression.

A child's risk for becoming depressed may increase with stress or with an experience of devastating loss or trauma. Behavioral problems and other psychiatric disorders—for example, conduct, attention-deficit, learning, anxiety, and substance abuse disorders—frequently co-occur with depression and may help explain its onset. A family history of depression or bipolar disorder is also a significant risk factor for depression in a child or young adult.

Because of the severity of the disorder, the AACAP and the APA support treatments that have been shown to be effective in reducing the symptoms of depression and promoting normal development.

b. Antidepressant Medications as Part of Effective Treatment

Medication, specifically antidepressants, can be helpful and even lifesaving for some children who have complex psychiatric disorders such as depression. Medication is most effective when it is used as part of a comprehensive treatment plan, individualized to the needs of the child and family. All children and adolescents who are taking antidepressant medication should be monitored closely by a physician, especially early in the course of treatment, or when medications are being changed or dosages adjusted.

Findings from the NIMH-supported Treatment of Adolescents with Depression Study (TADS) show that a combination of medication and therapy, specifically, Cognitive Behavioral Therapy, or CBT, are more effective than either option used alone. Family therapy and/or work with the child's school may also be appropriate components of a treatment plan. All interventions have potential risks and benefits, and parents need and deserve access to as much information as possible in order to make fully informed decisions regarding treatment options. It is important to remember that the majority of children and adolescents with depression who are not identified and treated are likely to have ongoing problems in school, at home and with their friends. Research indicates that more than half will eventually attempt suicide, and an estimated 2 to 5 percent will ultimately die as a result (Formbonne, E., et al.).

At the end of this testimony is an overview from ParentsMedGuide.org of depression treatment effectiveness, design of clinical trials and data reporting which sheds additional light on reports of suicidal thoughts by depressed adolescents.

c. SSRIs, Suicidal thoughts and FDA post-market actions

Many psychiatrists, patients and families have found the SSRI antidepressants to be extremely helpful for children and adolescents with depression when they are used in a well-monitored treatment program. In addition, the current evidence does not suggest that these medications increase the risk of suicide. It warrants emphasis that in the data from the clinical trials that the FDA analyzed, which involved more than 4,400 youth with depression, there were no actual suicides.

It does appear that these medications may increase the likelihood that a patient will actually tell someone about their suicidal thoughts or even about a suicide attempt. From my perspective, as a child and adolescent psychiatrist, this is actually a good thing, because it means you have the opportunity to intervene and to keep the person safe. I believe this is why none of the studies have demonstrated any increase in actual deaths from suicide in conjunction with the use of these medications. On the contrary, the adolescent suicide rate in the country has actually declined by over 25 percent since the early 1990's, in a manner consistent with the increased use of SSRI antidepressants.

We are concerned that the available research findings do not support a warning that may be misinterpreted by some practitioners or parents to mean that antidepressant medications actually cause children and adolescents to commit suicide. Such a conclusion is simply not supported by the data.

The AACAP and the APA supported both the FDA's evaluation of the safety data found in clinical trials of SSRIs and the Columbia University reclassification project, and we continue to support the public discussion of the resulting analyses. We also agreed with the FDA's decision to insert warning language with all antidepressant medications to alert physicians and families to the need to monitor for signs of new suicidal thinking or activity during treatment, although we feel that the specific nature and frequency of such monitoring should be based on the clinical needs of the child.

Both AACAP and APA did not, however, agree with the action ultimately taken by FDA in October of 2004, to require a "black box warning" on all antidepressant medications prescribed for children and adolescents. We were concerned—and recent data substantiates our concern (such as Medco Health Systems data which indicates that from 2003 to 2004, there was a significant decrease in the rate of SSRI prescriptions for children and adolescents) (Fields) that such a warning might inadvertently create a greater risk by discouraging families from seeking treatment and by dissuading physicians from the appropriate prescribing of these medications.

We are pleased that the FDA recently modified, with scientific input, the specific language used in the warning to more accurately reflect the actual research findings. The FDA decided to remove language that maintained that a causal relationship between medications and increased suicidality had been established. It also is

significant that FDA added the language “in clinical trials” when discussing the findings on suicidal thinking and behavior. In doing so, they are acknowledging the challenges and complexities associated with the translation of research finding into clinical practice. We hope the FDA will be willing to consider further modifications to labeling, package inserts and medication guides as more data becomes available.

2. Further Post-Market Research Needed

The AACAP and the APA call for new research on SSRIs to ensure that these medications are used in the safest and most effective manner possible. We support research efforts now underway, such as the NIMH Treatment of Adolescent Suicide Attempters (TASA) study and the NIMH supported Child and Adolescent Psychiatry Trials Network, a large simple trials network.

The recently reauthorized Best Pharmaceuticals for Children Act (P.L. 107-109) and the Pediatric Research Equity Act (P.L. 108-155), which codifies the 1998 Pediatric Rule, will ensure that pediatric clinical trials will be included during the development of new therapeutic medications, providing child and adolescent psychiatrists with additional safety and efficacy information about new medications. We also suggest Congress consider the creation of an independent body to oversee and advise the FDA on post-marketing issues.

3. Create a Central Nervous System Pediatric Advisory Committee

To provide the FDA with critical expertise on pediatric psychopharmacology, the AACAP and APA support the creation of a Central Nervous System Pediatric Advisory Committee that would be composed of child and adolescent psychiatrists, pediatric neurologists and other experts. This committee would work to improve the quality of life for the millions of children and adolescents with mental illness and their families.

We are pleased that the Pediatric Research Equity Act strengthened the FDA pediatric research efforts by creating a Pediatric Advisory Committee. While this committee will represent general pediatric research issues, the FDA also requires specialized guidance in pediatric psychopharmacology from experts in child and adolescent mental health and neurology. Pediatricians are not specifically trained in child and adolescent psychiatry or child neurology, and we should not expect general pediatric experts to be able to provide the FDA with the highly specialized expertise in child and adolescent mental illnesses required in pediatric psychopharmacology.

4. Workforce and Access Issues

Family practitioners are more likely than either pediatricians or psychiatrists to prescribe stimulants and less likely to use diagnostic services, provide mental health counseling, or provide follow-up care (U.S. Surgeon General Report). This is also true for antidepressants. Child and adolescent psychiatrists are the only medical specialty fully trained in the diagnosis and treatment of children’s mental illnesses, yet there are only approximately 7,500 of these specialists in the U.S. We encourage committee members to support the enactment of the Child Health Care Crisis Relief Act sponsored by Senator Jeff Bingaman.

These bills will help remove one of the main barriers to appropriate treatment for children and adolescents with emotional and behavioral disorders through the creation of educational incentives and Federal support for children’s mental health training programs. It will authorize scholarships, loan repayment programs, training grants, and specialty training program support. Children’s mental health professionals covered under the bill include: child and adolescent psychiatrists, child psychologists, school psychologists, school social workers, school counselors, psychiatric nurses, social workers, marriage and family therapists and professional counselors.

In addition, access to appropriate mental health treatment for children and adolescents requires the elimination of discriminatory policies and practices with respect to health insurance coverage. For this reason, both the APA and the AACAP fully support the passage of parity legislation at both the State and Federal levels.

Summary of Recommendations

The AACAP and the APA make the following recommendations:

- Enhance the release and dissemination of data from clinical trials through the development of a centralized, publicly-accessible, national registry.
- Strengthen post-market surveillance and reporting, and provide funding for more short-term and long-term pediatric clinical trials, including follow-up studies, on all medications prescribed for children and adolescents.
- Create an FDA Central Nervous System (CNS) Pediatric Advisory Committee composed of child and adolescent psychiatrists and child neurologists to provide FDA with expertise on pediatric psychopharmacology. Also consider the creation of an independent body to oversee and advise the FDA on post-marketing issues.

- Pass legislation to increase the number of children's mental health specialists available to study and treat disorders such as childhood and adolescent depression, including the "Child Healthcare Crisis Relief Act" sponsored by Senator Bingaman, and the "Children's Compassionate Care Act of 2005" S. 174 sponsored by Senators DeWine, Dodd and Murray.

Conclusion

The AACAP and APA appreciate this opportunity to submit testimony on the FDA's approval process as it relates to pediatric antidepressants. Both organizations are eager to work with Members of Congress to address the issues related to research into childhood mental illnesses and the training, treatment and services needed to assure that children with psychiatric disorders receive the appropriate and effective intervention that they need and deserve.

Endnotes from written testimony:

Birmaher B, Ryan ND, Williamson, DE, et al. (1996). Childhood and adolescent depression: a review of the past 10 years. Part I. *J Am Acad Child Adolescent Psychiatry*, 35(11), 1427-39.

Fields, Helen, "Sad kids: Antidepressant prescriptions fall for the under-18 crowd," U.S. News and World Report, February 4, 2004.

Kochanek KD, Murphy SL, Anderson RN, Scott C. Deaths: Final data for 2002. *National vital statistics reports; vol 53 no 5*. Hyattsville, Maryland: National Center for Health Statistics. 2004.

U.S. Department of Health and Human Services. Mental Health: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health, 1999.

FROM THE PARENTSMEDGUIDE.ORG

Overview of treatment effectiveness and suicidality

The effectiveness of treatment was demonstrated recently in a definitive study supported by the National Institute of Mental Health (NIMH). The Treatment of Adolescents with Depression Study (TADS) (March, J et al) showed that a combination of fluoxetine (Prozac®) and cognitive behavior therapy (CBT) led to significant clinical improvement in 71 percent of moderately to severely depressed adolescent patients. Improvement rates for other treatment groups in the study were 61 percent for fluoxetine alone, 43 percent for CBT alone, and 35 percent for placebo. This finding replicated two previous positive studies in pediatric populations (Emslie GJ, Rush, et al), (Emslie GJ, Heilgenstein JH, et al).

A key finding of the TADS concerned the positive impact of treatment on suicidal thoughts and behaviors, or "suicidality," in depressed youngsters. Suicidal ideation is a key symptom of major depression. It is typically present before the start of antidepressant treatment and is one of the major symptoms targeted for treatment. Since mood disturbances often are among the last symptoms to remit in treatment, and because antidepressant medications typically require several weeks to exert a clinical effect, the initial changes in brain functioning brought about by treatment are often not adequate to suppress suicidal thoughts. In the event that worsening might occur, the physician, in collaboration with the child's parents or other family members, must appreciate the importance of intensively monitoring a pediatric patient to assure patient safety during the early stage of treatment. In some instances, hospitalization may be necessary, although the vast majority of patients respond to outpatient treatment.

Against this backdrop, it is noteworthy that in the TADS, 29 percent of the depressed young patients reported having clinically significant suicidal thoughts at baseline. At week 12, the number of youth reporting any suicidal ideation had declined to 10 percent. Because youngsters who were most suicidal were excluded from the TADS sample, the proportion reporting suicidal thoughts when the study began was substantially lower than rates of suicidal ideation found in the community samples cited above (reference #3) of youth with major depressive disorder.

Without appropriate treatment, the consequences of depression are extremely serious. Four of ten youth will have a second episode of depression within 2 years. (Lewinsohn PM, et al.) They are also at increased risk for substance abuse, eating disorders, and adolescent pregnancy. (Kessler PC, et al.) Research indicates that over half of depressed youth will eventually attempt suicide, and an estimated 2- to 5 percent will die by suicide in the 10 to 20 years following an initial episode. (Fombonne et al.).

What prompted the FDA warning in September of 2004?

In 2004, the FDA reviewed 23 clinical trials involving more than 4,300 child and adolescent patients who received any of nine different antidepressant medications. (Hammond). No suicides occurred in any of these studies. Most of the studies that the FDA examined used two measures to assess suicidal thinking and behavior.

(1) All used "Adverse Event Reports," which are reports made by the research clinician if a patient (or their parent) spontaneously shares thoughts about suicide or describes potentially dangerous behavior. The FDA found that such "adverse events" were reported by approximately 4 percent of all children and adolescents taking medication compared with 2 percent of those taking a placebo. One of the problems with using this approach to measuring suicidal thinking is that most teenagers do not talk about their suicidal thoughts unless they are asked in which case no report is filed. (Gould MS, et al.)

(2) In 17 of the 23 studies a second measure was also available. These were standardized forms asking about suicidal thoughts and behaviors completed for each child or teen at each visit. In the views of many experts these measures are more reliable than event reports. The FDA's analysis of the data from these 17 studies found that medication neither increased suicidality that had been present before treatment, nor did it induce new suicidality in those who were not thinking about suicide at the start of the study. In fact, on these measures, all studies combined showed a slight reduction in suicidality over the course of treatment. Although the FDA reported both sets of findings, they did not comment on the contradiction between them.

Hence, the 2 percent and 4 percent spontaneous report rates need to be understood in the context of findings from community samples cited previously in which as many as half or more of teenagers with major depression are thinking about suicide at the time of diagnosis and some 16 percent to 35 percent have made a previous suicide attempt.

Although only nine medications were re-examined in the analysis, the FDA applied the labeling changes to all antidepressant medications. This was done on the basis of the advisory committee's perception that currently available data are inadequate to exclude any single medication from being potentially associated with the same increased risk for spontaneous reports of suicidal thinking and/or behavior found in the 23 studies.

Suicidality in adolescence

Suicidal ideation and suicide attempts are common in adolescence and do not have the same prognostic significance for completed suicide as those behaviors in later life.

The Federal Centers for Disease Prevention and Control, or CDC, reports that 17 percent of adolescents think about suicide in a given year. (www.cdc.gov) Among high school students, 12 percent of girls and 5 percent of boys attempt suicide in a given year. Ultimately, 2 per 100,000 girls and 12 per 100,000 boys die as a result of such attempts—a ratio of attempts to completed suicide that is 6,000 to 1 among girls and 400 to 1 among boys. In the U.S., this translates into approximately 2000 young people who die each year as a result of suicide.

Fortunately, the overall rate of suicide in the 10–19 year age range has declined by 25 percent over the past decade. Since this decade has been associated with a dramatic increase in the prescription rates of the newer SSRI antidepressants, a recent study has demonstrated that a 1 percent increase in prescription of antidepressant medication was associated with a 0.23 per 100,000 decrease in adolescent suicides (Olfson, M. et al.)

It is important to consider clinical trial data in the context of these population-based data. In its review of 23 clinical trials involving child and adolescent subjects who received any of nine different antidepressant medications, the FDA combined the rates for suicidal thoughts and suicide attempts under the general term "suicidality." This has fostered a public impression that there is a high rate of suicide attempts or even completed suicides in children and adolescents that can be attributed to taking antidepressant medication; in fact, suicidal thoughts and actions decline with medication and psychotherapy treatments, and there were no completed suicides in the studies reviewed by FDA. Suicidal thoughts or attempts do not equal suicides.

Every suicide is a personal tragedy that may be linked to inadequate treatment monitoring or severe adverse side-effects of a medication. Yet the rise in overall population treatment rates with antidepressant medication has not been associated with a rise in completed suicides in the larger population—in fact, there has been a substantial decrease in completed suicides over the past decade. Likewise, the higher spontaneous reports of suicidal ideation and attempts (referred to by the FDA as "adverse events") in children on antidepressants compared with placebo, has

not been correlated with systematic assessments of suicidal ideation or attempts increasing with these medications. Research is needed to determine how the relatively low rate of spontaneous reports of adverse events is related to the much higher systematically assessed rates of suicidal ideation and attempts, and which more clearly indicate a risk for completed suicide.

In an illness where unwanted and spontaneous suicidal thoughts are integral symptom components, treatment that increases communication about these symptoms can lead to more appropriate monitoring and decreased risk for the adverse event of greatest concern—i.e. completed suicide.

Endnotes from ParentsMedGuide.org

March J, et al (2004). Fluoxetine, Cognitive Behavioral Therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA* 292(7), 807-820

Emslie GJ, Rush AJ, Weinberg WA, et al. (1997). A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch General Psychiatry* 54(11), 1031-37.

Emslie GJ, Heiligenstein JH, Wagner KD et al. (2002). Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 41(10), 1205-15.

Lewinsohn PM, Clarke GN, Seeley JR, and Rohde P (1994). Major depression in community adolescents: age at onset, episode duration, and time to recurrence. *J. Am. Acad. Child Adolesc. Psychiatry* 33 (6), 809-818.

Kessler RC, Avenevoli S, Merikangas KR (2001). Mood disorders in children and adolescents: an epidemiologic perspective. *Biol Psychiatry* 49(12), 1002-1014.

E. Fombonne, G. Wostear, V. Cooper, R. Harrington, and M. Rutter. (2001). The Maudsley long-term follow-up of child and adolescent depression. 2. Suicidality, criminality and social dysfunction in adulthood. *Br J Psychiatry* 179, 218-23; Rao M, Weissman M, Martin JA, Hammond RW (1993). Childhood depression and risk of suicide: a preliminary report of a longitudinal study. *J Am Acad Child Adolesc Psychiatry* 32(1), 21-27.

T.A. Hammad. Results of the Analysis of Suicidality in Pediatric Trials of Newer Antidepressants. Presentation at the FDA Center for Drug Evaluation and Research (CDER), Bethesda, MD. September 13, 2004. Available at: <http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologidDrugs>. Accessed January 5, 2005.

Gould MS, Velting D, Kleinman M, Lucas C, Thomas JG, Chung M (2004). Teenagers' attitudes about coping strategies and help-seeking behavior for suicidality. *J Am Acad Child Adolesc Psychiatry*, 43(9), 1124-33.

Available at <http://www.cdc.gov/HealthyYouth/YRBS/pdfs/trends-suicide.pdf>. Accessed 12/29/2004

Olson M, Shaffer D, Marcus SC, Greenberg T. (2003). Relationship between antidepressant medication treatment and suicide in adolescents. *Arch Gen Psychiatry* 60, 978-982.

The CHAIRMAN. Dr. Scott Gottlieb.

Dr. GOTTLIEB. Mr. Chairman, thank you for the invitation to appear before the committee. Today, I want to tell you why I believe the FDA's mission is becoming increasingly complex, but with this complexity has also come many new opportunities to improve medicine, and I want to tell you why I believe that, as the sophistication of FDA's mission continues to increase, so must the tools it uses for accomplishing its work, especially when it comes to drug safety.

To acquire these tools, FDA will need new resources that allow it to make better uses of advances and information tools for monitoring the safety of approved drugs. The good news is that FDA is doing some of these things right now, albeit in small pilot programs. The bad news is, I believe our current political discussion seems to ignore these opportunities in lieu of some more visible changes. These visible changes will have far less positive impact on drug safety and will limit the access to medicines. They will make drugs more expensive and less likely to reach patients who need them.

Mr. Chairman, we are living in a remarkable time of scientific progress. When I was at the Food and Drug Administration, the

Centers for Medicare and Medicaid Services, a lot of my time was spent looking at the policies these agencies followed in the evaluation of new medical technologies.

When you look at the technologies that have become available even over a short period of time, it becomes immediately clear that the improvements in health care follow a step-wise progression. The introduction of new medical technologies, the realization of better ways of practicing medicine or of avoiding illness, all leads to small improvements in medical care that, over time and aggregated together, give us major improvements in health.

You can see this, for example, in the strengthening of our understanding of how the immune system works and the advent of our ability to manipulate it in order to produce drugs that can replicate our own immune processes, like monoclonal antibodies.

Or even more recently, you see it in our improved understanding of the genetic basis of disease. Already, if you look at the early drug pipeline being submitted to FDA, the investigational new drug applications, you see many drugs that were derived in part or entirely through techniques of genomics and proteomics.

All of these new medical products are the result of advances in our science of biology. Past medical products have taken decades or even centuries to be made manifest on the heels of the scientific discoveries that enabled them. Today's FDA is already seeing the early applications of dozens of drugs derived wholly or in large part from science developed just several decades ago.

This acceleration in time between the development of science and the creation of products that capitalize on it is giving us an awful lot of new opportunity to find fundamentally better ways of treating disease, but it also presents the government agencies that evaluate new medical technology with a lot of challenges, especially the FDA.

More and more of the products the FDA is seeing are very novel, and as such, the agency has no reference point. So in more and more cases, regulators are embarking on new ground each time they pick up a new application.

In the old days, drugs worked through fairly similar mechanisms. Now the same review division, let us take the Cancer Division, can simultaneously be reviewing a monoclonal antibody, a antisense drug, a molecule targeted to a kinase receptor, a radiolabeled antibody, a cancer vaccine, and a traditional cytotoxic cancer agent, all on the same day. In fact, I remember talking to the head of the Division on just such a day.

On top of all this, the FDA has more factories to inspect, more patients using more of these medicines more quickly after they are first approved, and more potentially dangerous imports seeping through our borders.

I believe the scientific challenges posed by new medical products will continue to mount, but I also believe this is good news because novel drugs invariably give us novel ways to fight old disease and many of today's medicines are simply far safer and far more effective than those that came before.

But as the science gets more intricate and more advanced, our tools for evaluating it also need to get more creative. This is especially true when it comes to how we evaluate drug safety. Under-

standing the full scope of any drug's side effects is the challenge, especially understanding them early.

Every clinician who prescribes medicines has seen adverse drug reactions, the unintended and harmful effects of drugs. Human biology, after all, is conservative, meaning our bodies reuse a fairly small set of very similar molecular processes to get all our jobs done. It follows, then, that any drug that is active in blocking some molecular process in order to have its desired effect will also block the same molecular process in another part of the body, parts that could lead to unwanted side effects. So there is no such thing as a completely safe drug.

The FDA's job is not to guarantee 100 percent safety. It is to approve medicines with an appropriate risk-benefit ratio by removing unreasonably unsafe drugs when necessary. The baseline isn't the perfectly safe drug, but the drug with benefits that outweigh reasonable risks. This is how we maximize public health benefits of new medical products.

Patients are rightly angry about recent events because they want safety questions to be uncovered and resolved much sooner. They don't want to have to wait many years. The good news is there are better ways to achieve the environment of improved drug safety we all desire without sacrificing the scientific progress we all embrace.

In particular, information technology properly deployed will enable FDA to pursue fundamentally better ways to monitor the safety and effectiveness of new medical products after they are made available in the marketplace. These are things the FDA is already doing a little, but needs to be doing much more.

Right now, when it comes to drug safety, the FDA relies on others to undertake the time and cost of monitoring. This passive reporting system leaves FDA dependent on busy doctors to fill out lengthy reports.

So far, fixes to our system for monitoring drug safety have all focused on making this antiquated system work a little faster by adding only a veneer of sophisticated information tools. As a result, information is made available to FDA slowly and takes even longer to analyze by the agency's trained personnel.

FDA needs systems that allow it to collect more information about a drug's use in the real world, and in some cases, real-time clinical practice, and to use this information more effectively. This requires two simultaneous efforts: First, tools for detecting and collecting more safety information more quickly at the point of care in order to detect potential problems earlier; and second, resources for making better, more frequent use of practical clinical data culled from real-world use of drugs in order to conduct more precise and faster follow-up studies on the potential safety problems.

In conclusion, Mr. Chairman, FDA has already taken some steps to try and create more active and proactive surveillance tools. With improved resources for conducting this kind of surveillance as well as resources for conducting large, simple safety studies in collaboration with product developers and health care networks on newly-approved products, FDA can improve its safety monitoring without burdening the approval process. Thank you.

The CHAIRMAN. Thank you.

[The prepared statement of Dr. Gottlieb follows:]

PREPARED STATEMENT OF SCOTT GOTTLIEB, M.D.

Mr. Chairman, thank you for the invitation to appear before the committee. Today I want to tell you why I believe the FDA's mission is becoming increasingly complex. But with this complexity has also come many new opportunities to improve medicine. And I want to tell you why I believe that, as the sophistication of FDA's mission continues to increase, so must the tools it uses for accomplishing its work. Especially when it comes to drug safety.

To acquire these tools, FDA will need new resources that allow it to make better use of advances in information tools for monitoring the safety of approved drugs.

The good news is that FDA is doing some of the right things right now, albeit in small pilot programs. The bad news is I believe our current political discussion seems to ignore these opportunities in lieu of some more visible changes. These visible changes will have far less positive impact on drug safety, and will limit access to medicines. They will make drugs more expensive and less likely to reach patients who need them.

Mr. Chairman, we are living in a remarkable time of scientific progress. When I was at the Food and Drug Administration and the Centers for Medicare and Medicaid Services, a lot of my time was spent looking at the policies these agencies followed in the evaluation of new medical technologies.

When you look at the technologies that have become available, even over a short time, it becomes immediately clear that improvements in healthcare follow a stepwise progression. The introduction of new medical technologies, the realization of better ways of practicing medicine or of avoiding illness, all leads to small improvements in medical care that over time, and aggregated together, give us major improvements in health.

You can see this, for example, in the strengthening of our understanding of how the immune system works and the advent of our ability to manipulate it in order to produce drugs that can replicate our own immune processes such as monoclonal antibodies.

You see it when you look at the mortality statistics around breast cancer, where successive product introductions from Taxols to Aromatase Inhibitors to drugs like Herceptin, each had a small impact that over time and taken together, led to significantly better odds of surviving the disease.

Or even more recently, you see it in our improved understanding of the genetic basis of disease. Already, if you look at the early drug pipeline being submitted to FDA—the investigational new drug applications—you see many drugs that were derived in part or entirely through techniques of genomics and proteomics, the latter of which is the science of how genes make proteins to carry out all of our complex human processes.

All of these new medical products are the result of advances in our science of biology. Past medical products have taken decades and even centuries to be made manifest on the heels of the scientific discoveries that enabled them. Today's FDA is already seeing in early applications dozens of drugs derived wholly or in large part from science developed just several years ago.

This acceleration in time between the development of a science and the creation of products that capitalize on it is giving us an awful lot of new opportunity—to find fundamentally better ways to treat disease. But it also presents the government agencies that evaluate new medical technology with a lot of challenges, especially the FDA.

More and more of the products the FDA is seeing are very novel, and, as such, the agency has no reference point. So in more and more cases regulators are embarking on new ground each time they pick up a new application.

In the old days, drugs worked through fairly similar mechanisms. Now the same review division—lets take the cancer division—can simultaneously be reviewing a monoclonal antibody, an antisense drug, a molecule targeted to a kinase receptor, a radiolabeled antibody, a cancer vaccine, and a traditional cytotoxic cancer agent, the kind of drug that killed everything a little but hopefully killed the cancer cells a little more.

In fact, I remember talking to the head of the cancer division on just such a day. On top of all this, the FDA has more factories to inspect, more patients using more of these medicines more quickly after they are first approved, and more potentially dangerous imports seeping through our borders.

I believe the scientific challenges posed by new medical products will continue to mount, but I also believe that this is good news, because novel drugs invariably give us novel ways to fight old disease. And many of today's medicines are simply far safer and far more effective than those that came before.

But as the science gets more intricate, more advanced, our tools for evaluating it need to get more creative as well. This is especially true when it comes to how we evaluate the safety of new drugs.

Understanding the full scope of any drugs side effects is the challenge, especially understanding them early.

Every clinician who prescribes medicines has seen adverse drug reactions—the unintended and harmful effects of drugs. Human biology, after all, is conservative, meaning our bodies reuse a fairly small set of very similar molecular processes to get all of their jobs done. It follows that any drug that is active in blocking some molecular process in order to have its desired effect, will also block the same molecular processes in other parts of the body, parts that could lead to an unwanted side effect. So there is no such thing as a safe drug.

The FDA's job is not to guarantee 100 percent safety. It's to approve medicines with an appropriate risk-benefit ratio and remove unreasonably unsafe drugs when necessary. The baseline isn't the perfectly safe drug, but the drug with benefits that outweigh reasonable risks. Congress has given a lot of thought to the laws that set out these parameters, amending the FDA's statute more than a hundred times. The system that our resulting law contemplates always took measure of the simple scientific truth that there's no such thing as a completely safe drug. What have changed today are not the safety of medicines but the acrimony of our public discussion of these things.

Today, the data that medical reviewers at FDA receive in conjunction with the approval process for new products are from highly structured clinical trials, carried out on homogenous populations of patients that are carefully screened and pre-selected and then given new drugs under special protocols. There is little chance such trials will ever provide a complete review of how a new treatment will perform when it is used in a much broader variety of patients in real world clinical settings.¹

Recent proposals to lengthen clinical trials, or require them to include more patients, will add to their cost and hence the cost of drug development and eventually the list price of new drugs. It will limit access to new medicines. But it will not assuage today's safety concerns, and it will never unearth the kind of rare side effects that were eventually revealed with Vioxx, or even yesterday in the case of multiple Sclerosis drug Tysabri.

Patients are rightly angry about these events because they want safety questions to be uncovered and resolved much sooner. They don't want to have to wait many years.

The good news is that there are better ways to achieve the environment of improved drug safety we all desire, while not sacrificing on the scientific progress we all embrace. In particular, information technology, properly deployed, will enable FDA to pursue fundamentally better ways to monitor the safety and effectiveness of new medical products after they are made available on the marketplace.

These are things the FDA is already doing a little of, but needs to be doing much more.

Right now, when it comes to drug safety, the FDA relies on others to undertake the time and cost of monitoring by sending news of potential problems to the agency. This passive reporting system leaves FDA dependent upon busy doctors to fill out lengthy drug safety reports that are used by the agency to identify and track potential drug side effects.

Taken together, this passive reporting process is slow and expensive, and of course, woefully incomplete. Most of the reports FDA ends up receiving are actually delivered not by doctors, but by drug makers, who hear about side effects from physicians, often while on sales calls.

So far, fixes to our system for monitoring drug safety have all focused on making this antiquated system work a little faster, by adding only a veneer of sophisticated information tools. For example, more of the forms that doctors and manufacturers complete are now fully electronic. But doctors still have to take proactive steps to enter the information by hand and evaluated by time-consuming, human intervention.

As a result, information is made available to FDA slowly, and takes even longer to analyze by the agency's trained personnel. Very subtle side effects, especially medical problems that occur naturally in a large population can take years to recognize and fully understand.

FDA needs systems that allow it to collect more information about a drug's use in real world, and in some cases real time clinical practice, and to use this information more effectively. This requires two simultaneous efforts:

¹ Scott Gottlieb and J.D. Kleinke., Is the FDA approving drugs too fast? United States Food and Drug Administration. British Medical Journal, October 3, 1998, No. 3163, Vol. 317; Pg. 899.

First, tools for detecting and collecting more safety information more quickly at the point of care in order to detect potential problems earlier.

Second, resources for making better and more frequent use of practical clinical data pulled from real-world use of drugs in order to conduct more precise and faster follow-up studies of potential safety problems.

Both efforts require FDA to have better tools for collecting health information electronically and then using information tools to be able to access and manipulate this information.

As electronic medical records and other IT systems gain wider adoption in healthcare, these kinds of opportunities will be more easily accessible. It behooves us to implement drug safety reforms that envision and accommodate these opportunities, rather than implement more expedient but fleeting fixes to our current—inefficient monitoring system that are predicated on an old way of doing things.

Consider this scenario: A new drug is launched that has a certain rare toxicity to the liver. A real-time surveillance network might eventually be able to detect subtle elevations in the liver enzyme tests of patients who were started on the drug and also happened to have blood work drawn around the same time. If enough of these signals were detected, it might alert FDA that there is a potential liver problem, and allow the agency to intervene before a patient experiences more permanent harm.

Under our current system, such a side effect might go unnoticed until a few patients developed severe liver failure. Even then, it might have been hard to link the problem to the medicine without taking months to go back and review the medical record of many thousand of patients who were started on the same medicine.

While more widespread use of these systems requires greater adoption of electronic medical records, there is already a critical mass of these systems. A lot that can be gained by conducting real-time surveillance on the existing IT infrastructure inside many large healthcare networks and academic centers.

FDA has already struck collaborations with some of these networks, including the Veterans Administration hospitals and Columbia Presbyterian Hospital in New York. Expanding these efforts will require additional funding.

The second step is developing more proactive determination tools to complement better detection systems. These are information and analytical capabilities for evaluating potential safety signals and for establishing a causal link between a drug and a suspected side effect.

Efforts to make better use of electronic healthcare information to more easily conduct practical studies, for example, are already well underway inside FDA and need to be dramatically expanded on if our safety infrastructure is going to keep pace with the expanding scope of our scientific opportunities in medicine.

In conclusion, Mr. Chairman, FDA has already taken some steps to try and create more active and proactive surveillance tools. With improved resources for conducting this kind of surveillance, as well as resources for conducting large simple safety studies in collaboration with product developers and healthcare networks on newly approved products, FDA can improve its safety-monitoring program without burdening the approval process.

With all the advances recently made in the science behind discovery of new drugs, there is little reason we should not be investing commensurate resources in bringing 21st century science to the task of ensuring their safety.

The CHAIRMAN. Our next witness actually got trapped by the storm in Connecticut and will be testifying by way of teleconferencing, and that is Ms. Abbey Meyers. Ms. Meyers.

Ms. MEYERS. [By telephone.] Thank you, Mr. Chairman. I really appreciate the technology that the staff has used to allow me to testify, even though we are under about a foot of snow.

FDA has a formidable task. It regulates products that amount to 25 cents out of every dollar that the American consumer spends each year. And the recent crises about the withdrawals of the COX-2 inhibitors and childhood anti-depressants have shaken the public's trust.

Before 1997, only drugs for serious and life-threatening diseases were rushed through the approval process in 6 months. FDA calls this fast track or expedited approval or priority reviews. The remainder of the drugs, standard drugs, were reviewed within 1 year, and that process seemed to work very well.

FDA has two constituencies that it has to satisfy. First is basically healthy people who have temporary and usually benign health problems, like the common cold, or people with chronic diseases like arthritis that are not life-threatening. Those people are usually unwilling to take major medical risks.

Now, the people with very serious diseases are often willing to take more risks, such as cancer patients who very often have to take very toxic drugs. The point, though, is that they are given realistic information about those side effects and the risks and they make their choice based on the education from their doctor about what the risks are.

Clinical trials are fine when a company is studying drugs. It usually involves a very closely designed patient population that may not reflect the real world. But once a drug gets on the market, it is used by people who have other diagnoses and people who take other drugs and they can suffer unanticipated adverse reactions because they didn't show up in the clinical trials.

There should be more of an effort to require companies to do trials on more realistically diverse populations in order to minimize the surprise adverse events after a drug reaches the market.

Consumers want, and Senator Kennedy has been advocating for us since the late 1970s, and that is we need understandable medication leaflets with every prescription written in understandable language. We don't see, and we couldn't read it even if we could see, the labeling on drugs that is written in medical language. People, if they have this information, they gladly make their own risk-benefit decision.

FDA should have the authority to require labeling changes just as soon as they see new side effects that warrant it. Right now, they have to negotiate the changes and this can take months or even years, as we have just heard. They should be able to change labels immediately because doctors don't have the information and they continue to prescribe these drugs to the wrong types of patients.

We also need a permanent FDA Commissioner as soon as possible because no one really knows where the buck stops at FDA until that is done.

Appropriations for FDA have never been a Congressional priority. It is funded by the agriculture committees, not the health committees. So when Congress doubled the NIH budget a few years ago, it should have realized that if the NIH is successful, more innovative treatments are going to come through the FDA and that FDA would need more resources. Instead, FDA's increases in appropriations have not kept track with inflation.

FDA's performance since the PDUFA amendments in 1997 is measured by its speed in reviewing new drugs and not on the scientific quality of its work. User fees cannot be spent on anything other than new drug reviews. We believe that they should be able to use PDUFA funds for other things in reaction to health emergency, especially. The agency is grossly underfunded.

Enforcement authority is lacking at the agency and it can't set reasonable penalties. For example, the agency has the right to require drugs that are approved on the six-month priority review to have Phase 4 studies after the drug is marketed, and a lot of the

companies simply ignore that requirement and never do the Phase 4 studies. The only enforcement authority FDA has for Phase 4 studies is to take the drug off the market, and that would make the patient suffer much more than anybody else. So instead, they do nothing and they need a way to set realistic penalties.

Direct-to-consumer advertising, companies can print and broadcast inaccurate, misleading ads for weeks or months before the FDA reviews them, and by that time, the damage is done and millions of people have been influenced. This has to be changed. They should approve the ads before they broadcast or print it.

On safety surveillance, the Drug Safety Monitoring Board that has been proposed, we believe it should truly be independent and not composed only of government employees. And if you look at the President's proposed budget for 2006, it calls for a reduction of factory inspections. Those factory inspections are really what caused the flu vaccine catastrophe, so this should be remedied.

On transparency, the public is really demanding greater transparency. FDA is excessively secretive. They say they can't post to the public because everything is a trade secret. We really need to have a way to get consumers' questions answered at the FDA.

In summary, FDA is the most important public health agency in our Nation. It must be placed high on Congress's priority list. It must have greater enforcement authority and it must be given more resources to protect the public from future catastrophes.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

[The prepared statement of Ms. Meyers follows:]

PREPARED STATEMENT OF ABBEY S. MEYERS

Mr. Chairman, members of the committee, thank you for inviting me to testify today about the Food and Drug Administration's (FDA) approval process, drug safety and the concerns of patients. I would like to offer possible solutions to the growing controversy about the safety of medical products that are regulated by the FDA.

The National Organization for Rare Disorders (NORD) is a non-profit voluntary health agency dedicated to the identification, treatment and cure of rare diseases through programs of education, research, advocacy and services to patients and families. Because most patients with rare diseases have no or few treatment options, our primary goal is to encourage research and development of new "orphan" drugs and biologics and "humanitarian use devices" (HUD).

We are grateful to Congress, through the Orphan Drug Act and annual appropriations, for its support of those living with rare diseases. Today, there are 266 FDA-approved orphan drugs on the US market; and the National Institutes of Health (NIH) and the FDA are doing more to help us each year. However, there are more than 6,000 known rare diseases, so there is still much to be done.

The FDA is the Nation's watchdog for pharmaceuticals, biologics, medical devices, veterinary medicines, foods and cosmetics. These products account for about one-quarter of every dollar the American consumer spends each year. Yet, the FDA is given meager Federal resources to ensure that these products are safe and effective.

Recent health crises arising from FDA regulated products threaten to weaken the public's trust in the Agency. Some of these drug safety issues include:

- Cox-2 inhibitors, used to ease the pain of arthritis, have been found to cause increased rates of heart attack and stroke;
- Most antidepressants have inadequate proof of safety and efficacy in children, but they are commonly prescribed for this population even though most are not approved for use in children;
- The influenza vaccine shortage can be traced to a factory in great Britain that failed FDA inspection;
- Estrogen, taken by millions of women, has been found to cause increased rates of heart attacks and stroke; and,

- In late February, the FDA issued a warning that two new drugs for psoriasis, which are being widely used off-label on a chronic basis, have been associated with cancer and serious autoimmune diseases.

These problems follow other drug withdrawals in recent years that killed or endangered our citizens, such as Fen-Phen diet pills, the cholesterol drug Baycol, and the diabetes drug Rezulin.

The public is now asking some important questions. Could the FDA review process have discovered or anticipated these problems before the products were marketed? Once these drugs were on the market, could the FDA have acted to protect the public sooner in any of these or similar cases?

A key source of misjudgments by the FDA is a relative imbalance in the time allotted to review drugs for serious- and life-threatening diseases versus less vital pharmaceuticals. This has been aggravated by the user fee system and is complicated by the two different patient constituencies that the agency serves.

First, most of the public are generally healthy and require medicines for temporary and benign illnesses such as the common cold. They usually do not want to be exposed to risks. They want the FDA to ensure their treatments will be near to absolutely safe and reasonably effective.

The second segment of FDA's constituency is people with serious or chronic diseases such as rare diseases and cancer. These individuals want new treatments as quickly as possible and are often willing to bear substantial risks in exchange for possible efficacy. For example, cancer drugs are often known to be very toxic, but a person who may lose his or her life to cancer is usually willing to take highly toxic chemotherapy drugs and suffer horrendous side effects in exchange for a hope of recovery.

These disparate groups bring tremendous political pressure to bear on the Agency. On the one hand, the FDA is pressured to approve drugs quickly for very sick people, when the drugs have minimal scientific evidence. On the other hand, the Agency is compelled to review drugs with more deliberation to avoid risks for healthy people.

Unfortunately, most consumers do not know enough or have sufficient skill to perform sophisticated risk/benefit analyses applicable to their own situation. What appears on the official FDA approved "labeling" for a drug is rarely helpful. It is written in medical terminology and printed in tiny fonts. It is very difficult for patients to get accurate information that is readable and understandable without medical training.

Instead, on a day-to-day, drug-by-drug basis, patients must rely on their physicians to interpret whether a particular product is safe and efficacious for their particular circumstance. And both patients and physicians must rely on the FDA to weigh risks versus benefits, and to ensure that the marketed drugs are not unsafe or ineffective.

Another tension arises from the way that clinical trials are constructed in order to comply with the scientific method. In a perfect world, a clinical trial would be one in which all patients were completely identical in every regard, except who received the study drug and who got placebo. The double-blind, placebo controlled study does, in fact, bring us closest to knowing whether a drug is safe and effective. What we often do not learn from clinical trials is the safety and effectiveness of a medicine when used in the wider heterogeneous population for which it will ultimately be prescribed. Clinical trials are never true mirrors of the real world.

Once a drug comes to market, people who take other medicines and have other diagnoses will take the drug and they may suffer an unanticipated adverse reaction. This means that labeling changes are often needed after a drug reaches the market, but the FDA does not "tell" companies to add changes to their labels. They "negotiate" the changes with manufacturers. Meanwhile, more patients may suffer adverse events because doctors are unaware of the problems associated with that particular drug.

The FDA must be given the authority to require manufacturers to do things that will enhance patient safety without delay, and they especially need the authority to impose penalties if companies do not comply.

We see many other areas of concern, some of which represent serious problems. Congress should examine and then rectify these items:

FDA Commissioner

The FDA has had a Commissioner for only 18 months out of the past 4 years. This also means many of the top managerial positions at the FDA are vacant. This sends a sad and dangerous message that the public health is not a high priority to our government. Without a Presidentially-appointed, Senate-confirmed FDA Commissioner, no one knows where the buck stops.

Appropriations

I have been dealing with the FDA for over 25 years and no matter who is in the majority, funding for the Agency has never been a high priority to Congress. A major problem is that the Agency is not funded through any of the health-related appropriations committees. Rather, it is funded, for historical reasons, by the agriculture appropriations committees. There, FDA's funding must compete against fish farms, diseases of peach trees, and the tobacco subsidy. One father told me that the government spends more money researching the diseases of shrimp than the rare disease that is killing his two sons.

Furthermore, when Congress so generously doubled the NIH budget, no one seems to realize that the ultimate success of NIH research is the development of more treatments and cures (NIH Roadmap). So for every dollar Congress appropriated to the NIH, they should have increased the budget of the FDA. Instead, the FDA has suffered from meager funding increases and a higher reliance on user fees.

Measures of Success

Under the Prescription Drug User Fee Act (PDUFA), the FDA's performance is measured by its speed in reviewing new drugs, not on the scientific quality of its reviews. The Agency is not allowed to spend user fee revenues on anything other than new drug reviews, so it does not have enough funding for post-marketing surveillance of marketed drugs, nor to monitor pharmaceutical advertising.

Enforcement Authority

The FDA does not have adequate enforcement authority, and it cannot set reasonable penalties if companies violate regulations. For example, the FDA sometimes requires companies to conduct Phase 4 studies after a drug is on the market, the statutory penalty for non-compliance being the removal of a drug from the market. This would punish patients as much or more than it would a company. So the FDA continues to require Phase 4 studies, and the companies continue to ignore the Agency's directives.

Direct-to-Consumer Advertising (DTCA)

If the FDA sees a misleading television ad about a drug, it can require the ad to be pulled off the air. Unfortunately, the rules regulating DTCA for prescription drugs allow companies to print or broadcast their advertisements before the FDA review and approve them. So the harm is already done and millions of people have been influenced by the misleading ad before it is pulled off the air. The Agency needs adequate staff to monitor and review advertising BEFORE it is broadcast or printed.

We suggest that companies might be given a "safe harbor" if the FDA approves their advertisement before it is disseminated. Otherwise, they should suffer high civil monetary penalties if they circulate an ad that is misleading or inaccurate without FDA's pre-approval.

Safety Monitoring and Surveillance

In response to sharp criticism, the FDA recently announced the creation of an "independent" drug safety monitoring board made up of government employees. Rather, we believe it should be composed of medical and scientific experts from outside the Federal Government, and it should report directly to the Commissioner's Office, with FDA employees serving in an advisory capacity only. Consumers should also be well represented. Again, if the perception among consumers is that the Agency is beholden only to industry, it stands to reason that any decision coming out of this new safety monitoring board—composed of government employees only—would be considered suspect.

The post-marketing surveillance system currently in use is seriously flawed and needs to be reworked at every stage of the process. The current system relies on voluntary adverse event reports from doctors and hospitals, but it is generally agreed that only a fraction of the AE reports are ever reported. Again, the FDA has been mandated by Congress to monitor the AE database to detect any serious patterns, but funds were never appropriated for that purpose.

Given the authority to extract monetary penalties from industry when there are egregious violations of the law, the FDA could use those funds for post-marketing surveillance safety studies as well as DTCA monitoring.

Priority Reviews

Since user fees were instituted at the FDA, the Agency has placed undue emphasis on drugs that are not medically important. Beginning in the 1980s, through the first half of the 90s, priority reviews were given only to treatments for serious and

life-threatening diseases (applications were reviewed within 6 months, and sometimes faster). Standard reviews, averaging 1 year, were given to all other drugs.

Many consumer groups believe that expedited approvals should be reserved solely for serious- and life-threatening diseases. Drugs for non-life-threatening diseases and disorders should not be given fast reviews when there are many alternative treatment options available. As I mentioned earlier, the majority of consumers do not want to be exposed to serious risks in exchange for a temporary symptomatic benefit.

Transparency

The FDA is probably one of the most secretive government agencies that any consumer will ever have to deal with. Virtually everything about a drug is considered proprietary. Consequently, Agency officials will not talk with anyone about the drug unless the manufacturer gives them permission to do so. Today, consumers are demanding greater transparency. This is our government and the FDA is here for us. We should not have to write Freedom of Information letters to find out why there is a shortage of a medicine, or how many other people taking a specific medicine have suffered an adverse event. Doctors and patients need answers. The FDA's secrecy is inexcusable.

The industry counters with the argument that "trade secrets" can not be disclosed, but because of this insistence on secrecy, consumers become increasingly suspect that important facts that could affect their health are being purposely hidden. Why were the studies showing that antidepressants were safe for children published, while other studies of the same drugs showing that some children died, kept secret?

There is the perception among many consumers that the FDA is beholden only to the industry. True or not, the FDA decision-makers should be reminded that their decisions affect lives. They should be reminded that they are not the Defense Department with national security concerns. They should feel free to answer the concerns of consumers readily and factually.

Summary

The FDA is a critically important public health agency that regulates products consumed or used by every person in this country. Consequently, the Agency must be high on the list of Congressional priorities. Public health catastrophes would be less likely to occur if the Agency were substantially strengthened and had the full support of key congressional committees.

The FDA needs greater enforcement capabilities, and a substantial increase in funding to allow it to respond to public health emergencies. Its performance should be measured not on speed, but scientific evidence and excellence.

If Congress gives the FDA the tools, the Agency will secure the public's trust. For all the talk about less government and smaller government, the FDA is one area of government that the public wants more of, not less. People want assurances that the food on their table will not make them sick. They want to be confident that the medicines they take will enhance, not destroy, their health.

It is up to Congress to reinforce America's trust in the FDA, which guards our Nation from medical catastrophes. It is Congress' responsibility to work with ALL stakeholders to strike a balance between increased innovation and safety and efficacy. Thank you.

The CHAIRMAN. Mr. Schultz, I thank you for your patience and we look forward to your testimony.

Mr. SCHULTZ. Thank you, Mr. Chairman. I certainly appreciate the opportunity to testify on the important issues concerning the FDA's drug approval process that you have decided to have the hearing about today. I think it is useful to answer the question you posed by separating the agency's performance, first its performance in reviewing new drug applications, and second, its performance in monitoring drugs after they have been approved.

In terms of the review of new drug applications, whenever a drug is withdrawn from the market, the question is inevitably raised, did the FDA make a mistake, and, of course, that is an appropriate question. But the principal point that I would like to make is that the fact that a drug turns out to have serious safety problems does not necessarily mean that the FDA made a mistake. This is be-

cause of the necessary disparity between the number of people on whom drugs are tested and the number of people on whom they are ultimately used.

Typically, new drugs are studied in a population of about 3,000 people, and yet they may be ultimately used, as in the case of Vioxx, on millions of people. The small studies that are used for the basis of approval simply are not designed to detect rare adverse reactions, and I should say it is not realistic to increase the size of these studies to be large enough to detect those reactions. This is just something we have to live with in the drug approval process. And yet, these rare reactions become very significant when the entire population is potentially exposed to the drug.

The studies done before approval also are not capable of detecting relatively small increases of common adverse effects, such as heart attacks and strokes. These are obviously very, very serious, but because they are common, if you have even a 50 percent increase, it simply will not be detected typically in the studies done before drug approval.

Of course, it may be true that the FDA made mistakes with respect to Vioxx or any of the other COX-2 inhibitors and it is appropriate to investigate the question. But at this time, I personally am not aware of any evidence that FDA made a mistake in approving those drugs.

We do know that new drugs have more risk than drugs that have been on the market for a long period of time. This is because less is known about them, but it is a fact of life and should inform us on how drugs should be regulated after they have been approved, and that is the issue that I would like to spend the remainder of my time from my prepared statement.

My main message here is that there is work to be done, constructive work to be done in terms of monitoring drugs after they have been approved. Under the Prescription Drug User Fee Act, Congress gave FDA additional resources and set goals for making decisions on new drug applications. The FDA, I think, did a terrific job doing exactly what Congress asked, but as it focused its attention on new drug approvals, the postmarket program has languished, and today, there is a tremendous opportunity to improve drug safety by focusing on the monitoring and regulation of drugs after they enter the market.

I have got six specific proposals. I will go through them very quickly. I wish I could say they were all original, but after hearing the testimony of this panel and of the FDA, I am actually happy to be able to say that I think there is broad agreement on many of them and there is a real opportunity to make some progress.

First, the FDA needs to take a leadership role in educating patients about the inherent risks of drugs. I think Dr. Kweder said that FDA maybe didn't do a good enough job in the Vioxx case about getting information to physicians once there were early indications about the risk of the drug. But the publicity of these drugs, other COX-2 inhibitors, other drugs that we all know about, just underline what everybody in this room knows, which is that there are inherent risks to prescription drugs. Senator Hatch talked about this in his opening statement. But my feeling is many patients, particularly those who don't have serious disease, really

don't focus on this, and many doctors, as well, in prescribing drugs that maybe don't need to be prescribed, or that if they are new, maybe shouldn't be the first choice.

Second, FDA should consider limits on direct advertising to the consumer of prescription drugs. Today, the drug industry spends billions of dollars on this advertising and it is probably an important factor in the vast number of sales of newly-approved drugs, Vioxx, for example. This needs to be studied and limitations ought to be considered. One possibility is to limit this advertising in the first number of years the drug is on the market. Another is to require disclosure that in the case of new drugs there are going to be unknown risks.

Third, Congress should increase the resources for postmarket activities. The fiscal year 2006 budget for the Center for Drugs provides about \$500 million—this is the administration's request—about \$500 million for the drug approval process. About six percent of that is allocated for postmarket activities. I think that is insufficient and I think a lot of the other witnesses have agreed.

My last three points are very important. They relate to the agency's legal authority. As we know, before a drug is approved, the burden is really on the company to show safety and efficacy. But after it is approved, the dynamic really shifts and FDA ends up having the burden of showing the problem.

And so my fourth suggestion is that the agency be given authority to order changes in the drug label when there is new information. The FDA finds new information about a drug like Vioxx, it shouldn't just have the option of withdrawing the drug from the market or bringing a misbranding action. It ought to be able to order that the label be changed, and, of course, the company ought to be able to appeal that decision within the agency or in court or discuss it with the agency.

Fifth, Congress should give FDA authority to require manufacturers to conduct postmarket studies. This is both after the time of approval and after approval of new information comes forward.

And sixth and finally, Congress should consider giving FDA authority to limit drug distribution, and in some cases, to actually direct the doctors how to prescribe drugs.

Thank you very much for the opportunity to testify and I will be happy to answer any questions.

The CHAIRMAN. Thank you very much.

[The prepared statement of Mr. Schultz follows:]

PREPARED STATEMENT OF WILLIAM B. SCHULTZ

I appreciate the opportunity to testify on the important issues concerning the FDA's drug approval process. I have worked in this area as a public interest attorney, as a Congressional staffer, as an FDA official and now as an attorney in private practice. I have listened to criticisms that the FDA is too slow in approving prescription drugs and that it acts too quickly; that it approves too few drugs and that it approves too many; that it is too strict in controlling advertising and that it is too lax.

Today's hearing concerns important questions about drug safety that affect all patients who use prescription drugs. The recent studies about the safety of Vioxx and other COX-2 inhibitors have raised questions about whether the FDA is adequately carrying out its responsibility to protect patients from unsafe drugs. Essentially, the issues concern whether the FDA is doing a good job in: deciding whether to approve drugs; identifying drug safety issues that appear after a drug is approved; and monitoring drug advertising, particularly direct advertising to the consumer. Two other

issues that I think should be added to this list are whether the FDA should devote more attention and resources towards informing and guiding physicians about how to use drugs; and informing the public about the safety of drugs. I now would like to address each of these issues.

A. The Drug Approval Process

Chronologically, the first question is whether there are serious flaws in the evaluation of applications to market new drugs, and in particular whether drugs such as Vioxx should have been approved in the first place. The same question could be asked of drugs such as Baycol, the cholesterol-lowering drug that was withdrawn after it caused more than 30 deaths and thousands of cases of severe muscle disease, and fenfluramine, one of the drugs that comprised the combination diet drug known as "Phen-Fen," which caused thousands of heart defects. The first point to make is that just because a drug was withdrawn for safety reasons does not mean that the FDA made a mistake in approving it. This is something that many patients do not understand.

The reason that we sometimes find out about safety risks after the drug has been marketed is explained by the necessary difference in the number of people on whom new drugs are tested and the number of people who ultimately use those prescription drugs. Typically, new drugs are studied in a population of about 3,000 people. Such a study can detect drug-related injuries that occur at a rate of between one in 500 and one in 1,000. Yet, if the drug is used by 200,000 people, a serious adverse event appearing in as few as one in 10,000 people is very significant, since it would occur 20 times. If the drug is used in 2 million patients, which is not uncommon, these serious, adverse events would occur 200 times. For this reason, rare adverse drug reactions often can be identified only after a drug has been widely used. Common adverse reactions, such as the increase in heart attacks and strokes observed in the case of Vioxx, are even more difficult to detect during the clinical trials conducted during drug development.

On the question of whether the information learned about drugs that have been withdrawn over the last several years demonstrates that there are serious problems with the FDA drug approval process, my answer is that the case has not been made. Whenever a prescription drug causes death and serious injury, it is appropriate to ask whether the drug should have been approved in the first place. And it is appropriate to investigate that question. My point is that based on what we know today, I cannot identify any fundamental problems with the drug approval process at the FDA.

B. Drug Safety After Approval

The important issue, in my view, is whether, with appropriate resources and regulatory authority, the FDA could do a better job in monitoring and regulating drugs after they are approved. At the outset, it must be acknowledged that the FDA is taking a number of steps to address the criticism of how drugs are evaluated after they enter the market. The most significant initiative relates to how information gathered by the agency's Office of Drug Safety should be evaluated and how decisions about the safety of marketed drugs should be made. At various times, it has been suggested that a separate drug safety agency should be established or that at least a separate drug safety center should be established within the FDA. This is a very tricky problem. On the one hand, the drug reviewers will have the greatest knowledge about the drug and the data reviewed in connection with its approval. On the other hand, any system must guard against the tendency of any decision-maker to defend his or her decisions. In other words, the charge that the reviewer who approved the drug will have a tendency to defend that decision must be taken seriously.

I do not believe that the best approach would be to completely separate the post-market function from the new drug application approval function. But it is important to elevate the post-market group in terms of resources and status and to create a mechanism so that an official who did not make the decision to approve the drug in the first place is charged with resolving disagreements. It seems to me that the agency's recent announcements about restructuring the decisionmaking on post-market issues are a step in the right direction. I do not know whether they go far enough. It is important that their implementation be closely monitored.

I am also aware that important steps are being taken to make studies of prescription drugs publicly available and to allow a public airing of opposing view before agency advisory committees.

I would now like to turn to other steps that should be considered to strengthen the agency's post-market program.

1. The FDA Should Initiate Programs to Educate Patients about the Inherent Risks of Drugs and It Should Consider Restrictions on Direct Advertising to Consumers

a. Educating Patients about the Inherent Risks of Drugs

The publicity around Vioxx and the other COX-2 inhibitors has highlighted the inherent risks of virtually all prescription drugs. In some cases, these risks are known when the drugs are approved, but the FDA has made a determination that the benefits of the drug (in terms of treating disease, for example) outweigh its risks. Everyone is aware of severe risks of chemotherapy drugs used to treat cancer. It has also been estimated that approximately 10–15,000 people die yearly from gastrointestinal complications caused by non-steroidal, anti-inflammatory pain medications (such as aspirin and the prescription alternatives to the COX-2 inhibitors). Many prescription drugs have documented risks.

Other risks are not known, and in some cases the risks of a drug will never be identified because they simply cannot be detected. The FDA should take a leadership role in educating patients about the risks of drugs so that patients consider these risks when deciding whether to take prescription drugs. In particular, the FDA should take on the responsibility to remind physicians and patients about the additional risks of newly approved drugs and it should advise caution in taking drugs to which large numbers of patients have not yet been exposed.

b. Consider Limiting Direct Advertising to Consumers of Prescription Drugs

It is not uncommon for a drug to reach very high sales soon after entering the market. Often new drugs (with their inherently greater risks) are unnecessarily prescribed to patients. Until the mid-1990's, drug companies were effectively prohibited from advertising. Today the drug industry spends billions of dollars advertising directly to consumers, and it has been suggested that consumer advertising is an important factor in the increasing sales of prescription drugs, particularly new drugs entering the market place. This needs to be studied and limitations on consumer advertising should be considered.

One possibility is to ban consumer advertising for a period of time (one or two years) after a drug has been approved, as additional data are collected on the drug's safety. Another alternative is to require more explicit and more prominent disclosures about the safety of prescription drugs. In the case of new drugs, manufacturers could be required to include a standard disclosure about the inherent risks of new drugs.

2. The FDA Should Be Given the Resources and Authority to Establish an Effective Program for Monitoring Drugs After They Are Approved

One unfortunate consequence of the Prescription Drug User Fee Act ("PDUFA") is that the FDA's program for monitoring drugs after approval has languished while the Center for Drugs focused its energies on meeting the Congressional directives regarding new drugs. Understandably, in recent years, the agency's focus has been on getting drugs reviewed, but in order to meet PDUFA targets that a certain portion of the drug approval process be funded with Federal money, the agency has cut funds for post-market studies.

Congress should consider sending the FDA a strong message that it expects the agency now to turn its attention to monitoring, identifying and controlling adverse reactions to drugs on the market. This can be done by giving the FDA the resources and legal authority it needs to devise an effective post-market program.

In terms of resources, the fiscal year 2006 budget for the FDA's Center for Drugs is \$505 million, but only \$33 million is allocated for post-market activities, an increase of \$6 million over fiscal year 2005. This funding level is insufficient to adequately monitor drugs after they enter the market or to initiate studies if questions do arise. The resources could be made available through appropriations or by allowing the agency to use PDUFA funds for this purpose.

Congress should give the FDA adequate legal authority to act when it obtains information about a drug on the market. In essence, before a drug is approved, the company that has the burden of establishing safety and effectiveness. As a practical matter, the FDA has the upper hand in deciding whether to approve a drug and in deciding on the content of the drug's label. Once the drug enters the market, the dynamic changes. Now the company has the upper hand. Some of my suggestions are designed to give the agency more authority after the drug is approved and to make it clear that the company has the continuing obligation to demonstrate the safety and efficacy when new data become available raising questions about the safety of the drug.

a. Authority to Order Changes to the Drug Label Based on New Information

All known information about the safety of a drug is supposed to be included on the drug's label, and the FDA has sufficient leverage to require appropriate information at the time the drug is approved. The problem comes when new information is discovered after the drug is already on the market. When that occurs, there is no explicit authority for the FDA to order that the label be changed to include new information or new warnings. The FDA's only recourse is to withdraw the drug from the market or to bring a misbranding action. These options are usually inappropriate and cumbersome. Thus the FDA is left to negotiate labeling changes with the company and it does not have sufficient leverage to require the changes that it deems appropriate.

Congress gave the FDA the authority to order appropriate changes in the labeling of prescription drugs. This authority could be used if the agency reaches an impasse in discussions with the drug manufacturer. This new authority should be accompanied by the opportunity for the affected company to appeal a decision with which it disagrees, administratively and in the courts, but ordinarily implementation of the changes should not be delayed while any appeal is pending. Finally, the agency should have authority to require the manufacturer to notify physicians of important labeling changes.

b. Authority to Require Manufacturers to Conduct Post-market Studies

When the FDA approves a drug, there are often unanswered questions that need to be studied. In other cases, these questions become apparent only after a drug is approved. Today, the FDA sometimes obtains commitments from companies to undertake post-market studies as a condition of approval, but often the companies do not fulfill those commitments, and the agency's legal authority to require the studies is questionable at best.

The FDA has the authority to require post-market surveillance of medical devices, but oddly it never has been given this authority for prescription drugs. The law should be amended to give the FDA the explicit authority to require companies to conduct post-market surveillance of prescription drugs, both at the time of approval and after the drug has been approved.

c. Authority to Address Misuse of Drugs by Physicians

The FDA should actively intervene when physicians misuse drugs. It is almost gospel at the FDA that the agency does not interfere with the "practice of medicine." This means that once a drug is approved for a single use, physicians are free under Federal law to prescribe it for any use. Sometimes off-label uses are appropriate and represent good medical care. Other times, these unapproved uses can become widespread and dangerous.

In some instances, physicians have ignored the FDA's directions, risking the health of their patients. For example, the FDA has approved the drug Accutane only for treating severe acne. Accutane is very effective, but it causes deformities in 25 percent of children born to women who take it during pregnancy, and strong warnings have not been enough to discourage physicians from limiting its use. For years, evidence has accumulated that physicians prescribe Accutane for moderate and mild forms of acne. The FDA should be given the legal authority to limit physicians' use of drugs when deviations from FDA-approved uses can lead to severe injuries. This should include explicit authority to limit the distribution of drugs to certain specialties. The authority to require physicians to follow important label directions also should be considered.

As an observer and for a time as an insider, one thing that is clear to me is that The FDA listens very carefully to Congress. An excellent example of this is the Prescription Drug User Fee Act, first enacted in 1992. Before PDUFA, there were endless articles in newspapers and scientific journals accusing the FDA of denying sick people drugs that they desperately needed, while at the same time those drugs were available in Europe and other developed countries. According to these charges, the FDA was responsible for the "drug lag." Congress passed PDUFA because user fees were seen as the only realistic method of increasing the funds for reviewing prescription drugs, thus eliminating the delays that could be attributed to inadequate funding. As a result, drug review times have been cut in about half, so that today the FDA makes decisions on drugs that represent important advances in medical care in 6 months and on all drugs in 10 months. It can no longer be said that the United States is the last country to approve important prescription drugs; more often we are the first.

As with the drug lag, there is significant room for improvement in our system for monitoring drugs after they enter the market. With an appropriate direction from Congress in the form of adequate resources and legal authority, the FDA could make significant progress in identifying the risks of drugs after they enter the market.

Thank you very much for the opportunity to testify. I would be happy to answer any questions.

The CHAIRMAN. I want to thank the entire panel for their depth of knowledge and their willingness to share it with us. I want to assure you that your entire testimony will be part of the record. I want to particularly thank those who did kind of executive summaries. Sometimes it is a little easier for me to get my colleagues to read the executive summaries than it is the whole testimony, but there will be people looking in-depth at all of this information. It is not only critical, it is kind of a hot issue right now, which always stimulates Congress to do a little bit more.

Dr. Fleming, in your recent Health Affairs article, you note that while there is interest in accelerating FDA's approval to allow potentially life-saving new treatments to come to the market, caution should be exercised not to compromise reliable and timely evaluation of the safety and efficacy of the new treatments. My question to you is, how do we exercise the right level of caution? How do we appropriately weigh the timely access and safety?

Mr. FLMING. Senator Enzi, this is certainly a very challenging issue. The Subpart (h) accelerated approval process has been established to allow the public to get earlier access to interventions that are promising in life-threatening disease settings where there is a considerable unmet need.

While that, in fact, has very significant potential benefits, the risks that are incurred in that process are that we could end up having fairly extensive marketing of products where we don't yet know reliably whether or not an agent that has a biological effect—shrinking a tumor, which, for example, is hopefully going to ultimately lead to clinical benefit to the patient, reducing symptoms or prolonging survival—we don't know for certain whether or not that relationship truly exists. Meanwhile, we have lesser amounts of safety experience because the accelerated approval process allows for the marketing of the product based on lesser benefit-to-risk information than you would have for full approval.

So the challenge or the difficulties here are that once a product is in the market, it is often very much more difficult to now complete the clinical trials that will reliably tell us whether or not this intervention truly has a favorably benefit-to-risk profile. Patients are less willing to go on to randomized trials. Sponsors will tend to have a lesser sense of urgency to get these studies done in a timely way.

And so the results of this is, in many instances, while the intention had been to allow earlier access while the validation trials were being completed in hopefully what would be a very timely way, this can turn out to be a very extended time period. And then when those validation studies are complete, the difficulty is very often they are not persuasive and the agency is put in a very difficult position, and I believe Congress and the agency need to have a clear sense of a pathway to be followed when those validation trials are not, in fact, conclusive.

The bottom line is, as I had mentioned in my comments, what is extremely important here is that we need to have policies to ensure that products that are, in fact, being used under an accelerated approval do not, in fact, have an extended period of time of

being used where we could, in fact, be putting patients at risk of having greater safety concerns than efficacy. There needs to be a clear procedure here to ensure that the validation trials are completed in a timely way and that if they aren't, in fact, conclusively favorable, that the product doesn't end up being marketed for an extended period of time.

The CHAIRMAN. Thank you. Dr. Fassler, public discussions focused on adverse drug events, increased suicidal thinking and behavior in pediatric patients, particularly treated with the SSRI anti-depressants. Few have commented about the bad outcomes that may occur if the black box warning unintentionally discourages prescription of the drug for children who might benefit significantly from its use. What is the practical effect of the black box warning?

Mr. FLEMING. Senator, we have recently received data which indicates that there has been a very significant decline in the prescription rate for these medications across the country, and that is of concern. This happened over a very short period of time. My concern is, are kids who actually have depression getting the appropriate treatment that they need and deserve?

This is a very serious illness, as you noted. Forty percent of kids who have depression go on to have a second episode within 2 years, and we know that appropriate treatment, including treatment with medication, significantly reduces that relapse rate. Over half of the kids with depression will eventually attempt suicide, the follow-up studies have demonstrated to us, and between two-and-a-half and five percent of these kids will ultimately die as a result of these attempts. So this is a very serious illness.

I would ask some of my colleagues on the panel to see this rapid shift in prescription patterns across the country as very concerning. I think all these kids really need evaluations. We need to make sure that they actually have the disorder. But I am concerned that the action that we have taken has unintentionally frightened some parents and just made them less likely to get help for their kids with problems like depression.

I also know from my own experience and from talking to colleagues across the country that, in particular, a number of pediatricians and other primary care physicians have become increasingly hesitant to prescribe these medications. Although these physicians have not had full training in the diagnosis and evaluation of psychiatric disorders, they are integral members of the treatment team for these kids. We really need them to be working with us.

So we need to be monitoring this extremely carefully. I mentioned in my testimony that the adolescent suicide rate has actually declined over 25 percent since the early 1990s. This is very good news and it will be devastating if we start to see that rate climb back up again because we have made this decision.

The CHAIRMAN. Thank you. My time has expired.

Senator Burr.

Senator BURR. Thank you, Mr. Chairman.

Dr. Fleming, your number five proposal establishes an FDA program for observational studies and clinical trials. Real quickly, could that be done extramurally or would that have to be solely done within the FDA?

Mr. FLEMING. Senator Burr, this is certainly an important issue. We clearly need to have collaboration in all sectors in order to be able to have the type of information in a timely way about potential safety risks. I think, as Mr. Schultz had pointed out in his commentary, as well, the FDA needs to have the authority and the ability in those settings where these types of observational studies that need to be done aren't being done by the industry or by NIH, are completed.

Senator BURR. Can we accomplish that through academia—

Mr. FLEMING. Academia can—

Senator BURR. Through extramural—

Mr. FLEMING. Academia can and does contribute, and yet the reality is, there needs to be a mechanism to empower the FDA to more broadly have the ability to have these large-link databases, which in the COX-2 inhibitor setting were an important mechanism to be able to identify safety signals. So we need to enhance what is—

Senator BURR. I think we all agree that the larger the pool, the more information that is relevant we can get.

Dr. Fassler, you are interested in a publicly-accessible registry, you said for doctors and for patients. I just want to ask you to very briefly answer this. Do you believe that patients can fully understand the data that comes from a clinical trial or is that just a degree of openness that you feel you have to include if you are going to lobby for doctors?

Dr. FASSLER. Senator Burr, I am not sure that physicians can always understand the information that comes from clinical trials, but I do think that physicians, patients, and researchers really need access to this kind of information. You would be amazed how sophisticated a lot of patients are, and again, others on the panel can speak to this, who come to physicians who have really done a tremendous amount of research and do know a lot about—

Senator BURR. I think you ended on a very key point, and that is that patients who are faced with disease have learned to do a tremendous amount of education on their own, and electronically, there is nothing that is not at their fingertips, with the exception of the data. The question is, could they put it in the right context like a researcher, and I think that is a question mark that we have to leave out there.

But it does lead me to the heart of my next question, which is really to Bill Schultz. And by the way, let me thank you publicly for your service. You have gone above and beyond at the FDA, on the Hill. You have got a very varied background and it is a tremendous asset to have you here as a witness on this issue today because I believe that we are in a very delicate area as we talk about what we do next because there are some things, as witnesses have pointed out, that could have a devastating effect on certain populations that exist and their potential access, especially those patients who have a choice between nothing and nothing today.

So let me turn to you if I could, Bill. You raised two of your six points, educate patients of the risk. Why not doctors?

Mr. SCHULTZ. That is a big part of it, too—

Senator BURR. Do they not come before patients? I mean, are they not our conduit?

Mr. SCHULTZ. You know, it is interesting. By the way, I really appreciate your comments. They mean a lot. When the issue of direct advertising to the consumer first came up in really the late 1980s, my view—and I think I was asked to testify on this, and my view was you ought to allow it because you have the doctor in between the patient and the decision and that should be full protection. And it really should be. But the reality is, I think patients very often go to doctors and they get drugs when they shouldn't, and so it is really both.

Senator BURR. But the point that you make is educate patients, but limit direct-to-consumer advertising. The two contradict each other to some degree. Educate them only on what you want them to have, but don't educate them on the benefits of a pool of drugs, and I think that is an inconsistency that—it is a policy question that we have got to decide. There are up-sides and down-sides to every decision that we make. As I have covered with the FDA in their panel, the benefit of it is that we now have many patients across the country that are on cholesterol-busting drugs that are not bypass patients today that ultimately increase their quality of life and save us money in the system.

You also said the FDA should have the authority to limit drug distribution. Actually, limit doctors' ability to prescribe. I would like to ask you just to be a little more specific on that one. One of the challenges that we always have as legislators, and I think we look at FDA and other agencies, is that we are not here to practice medicine in a doctor's office. We are here to set the guidelines. And I think to some degree, I am confused with the blurring of the line there.

Mr. SCHULTZ. This is a tough one. I think the easiest place to look at is maybe the FDA ought to be able to limit in certain cases drugs to certain specialties. It is authority they have for medical devices. And so there may be certain drugs that they see that are just prescribed too widely and that it would be limited to certain specialties or certain types of doctors to prescribe.

Senator BURR. If you took that outside of the arena, though, that is one of the issues about off-label use today, is that because we tightly control what we are willing to let be on that label, doctors have more of a tendency when they find something that works that is off-label that they go to it.

Mr. SCHULTZ. Right.

Senator BURR. I understand the spirit in which you suggest it. It is a very—

Mr. SCHULTZ. It is a tough issue. I think we all recognize that off-label use in many cases is good medical care, but I think we also have to recognize that sometimes it isn't. I use the example of Accutane in my testimony, which is a very effective drug for severe cystic acne. FDA has done everything it can to basically tell doctors that is the only place it should be used, particularly in women, because it also creates a 25 percent risk of abortion if it is taken by somebody who is pregnant. They have had no luck. And so the question is, should they be able to do more in that kind of an extreme example?

Can I make a comment about direct advertising to the consumer?

Senator BURR. Yes, sir.

Mr. SCHULTZ. Because I think you raise some very good points. I think the benefit of it is it educates patients, and that is the plus. The negative in my mind, particularly for new drugs, is that it can vast increase the number of people taking these drugs, and maybe that is not a good thing in the first few years before we know very much.

And so what I suggest for consideration is perhaps in the first few years, it shouldn't be allowed for new drugs, or perhaps there ought to be an extra warning on new drugs to inform patients that really we know less about these products than we do about drugs that have been on the market for a long time.

Senator BURR. I am not sure DTC would be the subject of conversation if we didn't have as many ED advertisements on TV today from the industry, and that is something that we can take up.

Let me just point out, if I could, Mr. Chairman, that the wish by FDA now to create a more robust postapproval surveillance program is a change that is happening because I think that, Bill, when you were there, and we certainly pursued PDUFA, the focus was on the reporting by doctors. We are now at a different time. We have got to come up with a different system. It is my hope that we can get all parties to try to do something that is not only responsible, but addresses exactly what Ms. Davenport-Ennis talked about, and that is that you have got to make sure that you never forget that there is a population out there that is on the edge. How we handle this affects the degree of research and development that is done.

Even though I didn't have an opportunity to ask Ms. Meyers questions, some of the concerns that she expresses are amazing to me as a representative of the rare disorders because those are the ones that are affected most and first by the lack of research dollars going in when we make the world unpredictable. So at the end of this, it has to be predictable. I thank each of them. Thank you.

The CHAIRMAN. Thank you. Senator Isakson?

Senator ISAKSON. I apologize to the panel for being late.

Dr. Fleming, I would like to ask you, do you concur in general with Mr. Schultz's remarks with regard to advertising limitations?

Mr. FLEMING. I think the reality here is that we want to get the truth to the public. The advertising to the public in direct-to-consumer advertising is certainly one aspect, but in many instances, it doesn't reflect the essence of the truth.

One of the comments that I had made in my recommendations was to encourage the FDA reviewers to be more forthcoming in their communication. One experience that I have had on FDA monitoring committees, FDA advisory committees, is that it is striking how often what you read in the clinical literature is not fully capturing the essence of really what is known in the evidence about benefit-to-risk. There is what I call a sponsor spin in what gets into the clinical literature because much of what is written is influenced by academics and industry that have some conflicts of interest.

Certainly even more so, what gets presented in direct-to-consumer advertising can't be expected to be an independent, objective assessment of the truth. In some instances, particularly in settings where there are significant concerns about safety risk, as has been

identified by the COX-2s, there are real concerns, then, about direct-to-consumer advertising giving a misrepresentation of the true benefit of what is truly known about benefit to risk.

Senator ISAKSON. That being said, I take it that, in part, is some of the reason for your recommendation, the conclusions that the one thing we should not do is have an external review panel established, is that correct?

Mr. FLEMING. Well, part of my concern here is not only the fact that I think FDA brings the greatest overall insight into regulatory issues. Clearly, FDA is benefited greatly by having external advice from industry and from the academic community. And yet the reality is, there are conflicts of interest. I believe that it is one of the issues that concerns me, as to the influence of that on the objectivity of the input that would occur in that process.

Senator ISAKSON. Thank you. One last question of Dr. Fleming. In recommendation number three that begins, when a safety signal is found, frequently from noncontrolled postmarketing data, FDA should, and I didn't hear the testimony, so I apologize if I am behind the curve here, but that tells me or portends to me that a postmarketing situation is a drug that is already on the market, and then they get some notice that there may be a problem, or there was an episode or there were a sequence of episodes. What currently—your solution begs the question that currently, there is not a standard time line and methodology upon which that is measured and tested. Is that true or not true?

Mr. FLEMING. Well, I don't—I am not sure about the standard time line. What I know is that there is a clear recognition and acceptance that there must be postmarketing safety assessment, and there are many levels for that. As we have discussed, passive surveillance using MedWatch is useful at a certain level. More effective are large-link databases that allow us to more reliably get assessments of signals.

But ultimately, when you see those signals, the most reliable way to assess the degree of benefit and risk is through randomized trials, and my concern is there are settings, such as in the COX-2 inhibitors, where there is great need for having postmarketing randomized trials of sufficient size and duration that we are going to be able to detect safety risks that could be sufficiently rare that you wouldn't be able to reliably assess them except in the randomized trials, but could have the influence to tip the scale on benefit-to-risk. And I believe the FDA should have the authority in those settings to indicate that those studies should be done in a timely way.

Senator ISAKSON. Thank you very much. And not a question, Mr. Chairman, but a comment to Ms. Davenport-Ennis. I had the chance to skim most of your testimony, although I didn't get to hear it. I want to commend you on your advocacy in balancing safety and timeliness and also not thwarting research and development. Cancer survivors, of which my sister is one, from radical treatments and things like that appreciate the dynamics of the pharmaceutical industry and new innovation, and safety is important, but we have got to recognize the balance for those that life is in the balance at any one given point in time. So I appreciate your testimony.

Ms. DAVENPORT-ENNIS. Thank you.

Senator ISAKSON. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you. I am going to take a little chairman's prerogative and ask a few more questions. I will note that the record will stay open for an additional 10 days so that all members of the committee will have an opportunity to submit questions in writing, and hopefully you will provide us with the answers to those, plus any expansion on comments that you would like to make.

Dr. Gottlieb, some argue that the so-called "me-too" drugs raise costs while diverting R&D funds from true innovation. Should the FDA raise the bar for approving follow-on drugs, or are those drugs just an example of competition at work, generating lower prices and better products?

Dr. GOTTLIEB. Well, the reality is that the FDA does raise the bar for the approval of those drugs. When you look at second- and third-in-class drugs, the trial size is usually significantly higher than the first-in-class drugs. That is just a fact of life inside the agency.

But the other reality is that those drugs do provide a significant benefit to patients, not only differentiation between molecules that don't all have the same effect on patients, but also price competition. Study after study shows when there is multiple drugs in a class, that it does bring down the price.

Mr. Chairman, if I may just make one comment about the discussion here for mandatory authority to the agency for the requirement of trials, you know, people have discussed giving the agency the authority to require postmarket trials and require label changes. I think another fact of life inside the agency, with all due respect to my former colleagues who I have a lot of admiration for, is that the agency doesn't use its existing authority there very well. Very often, the first pass at label changes that the FDA works on aren't worded very well and the dialogue that goes on between the agency and sponsor results in a much better label change.

The same thing is true of the postmarket studies that the agency often proposes. These proposals are made very frequently late in the process, very close to the time of approval. They are sprung on the sponsor days before approval, sometimes even hours before approval, giving the sponsor very little time to have any give and take with the agency about what is a postmarket study that can be accomplished. That is why I think in some cases you have postmarket studies that are unrealistic, because the sponsor didn't have enough time to have that dialogue.

So I think the agency has the opportunity to use the existing authorities better and have a better dialogue about label changes and about postmarket studies with sponsors without the requirement to be able to mandate it. I think, in fact, mandating it will take away that dialogue and take away the opportunity to have the input from the sponsor, which more often than not results in a better product.

The CHAIRMAN. Thank you. Another question for you, though, because you are familiar with the agency's structure from your tenure as an FDA Senior Policy Advisor with Commissioner McClellan. Do

you believe that the FDA needs to be reorganized to separate the Office of Drug Safety from the rest of FDA?

Dr. GOTTLIEB. No, I don't. I think that is moving the issue of safety oversight in exactly the wrong direction. There are many reasons why I think the evaluation of safety needs to be integrated with the evaluation of efficacy. First of all, you can't measure safety outside of some kind of measure of what the benefit is of the drug in the postmarket. The reality is that both move in different directions. They move in the same direction in postmarket, but they do evolve.

A good example of this is the TNF inhibitors class of drugs that are used for rheumatoid arthritis, among other things. If you look at those drugs, if you take a static measure of their benefit and measure it against what we know about their safety today, you probably wouldn't approve them today because we have learned in the postmarket that they have many more risks than what we knew when they were first approved. But the reality is, we also know they have far more benefits than we knew when they were first approved.

So now when you look at them, when you line up today's notion of risk against today's notion of benefit from these drugs, it makes a lot of sense to have these drugs on the market. So you need to have both evaluated within the same context.

Just within the structure of the agency itself, I think removing the evaluation of safety and, in fact, creating a new Office of Drug Safety, as some have proposed, is going to make it harder to recruit good people into that function. I think any time you take a line of drug review outside of the management structure of the Center for Drugs and outside of their senior managers, who are the most accomplished people inside the agency, they have risen up the ranks to leadership positions, I think you get a worse result. I think the same would be true here if you tried to carve out drug safety and move it away from the Review Division.

And the reality is that having the drug safety integrated into the Review Division, I think reminds people every day, it gives them input every day to the safety parameters they need to be looking at, and again, isolating that, creating a separate entity, will just further remove that from the consciousness of the work that goes on every day inside the agency.

The CHAIRMAN. Thank you. Ms. Davenport-Ennis, under the current ethical guidelines, if the data are strong enough to indicate that a drug is safe and effective before the conclusion of a clinical trial, the trial is halted, the therapy is given to everybody in the trial. Some people have proposed long-term studies be required prior to approval of the drug. It seems to me that a long-term pre-approval study would run afoul of these ethical guidelines. How do you see these additional requirements intersecting with ethical guidelines for conducting clinical trials?

Ms. DAVENPORT-ENNIS. Thank you for the question. I think that on behalf of the patient, if we look at a drug such as IRESSA, we will take that, because there has been so much coverage about it in the United States. For lung cancer patients who were in the trial at the time that the drug was being tested and the results were so phenomenal during that trial, to bring the trial to conclu-

sion and allow that drug to go to market because those cancer patients had very few options of drugs that were available to them, indeed, I think, made sense, and from the patient perspective, the population was glad to get it.

At the same time, I think the fact that we continue to collect information about that drug and to report additional information around that drug was also beneficial to the patient community. I think at the end of the day, having an informed patient population also means that part of that information allows them to understand what the benefits are, what the risks are, and when they enter a clinical trial, I think most patients understand that there may accrue to them an added benefit if they choose not to be in one.

So I think my answer to the question on behalf of patients is it was a very good process and we are happy to see that it is available in the market.

Mr. Chairman, if I may, may I also hazard a response to a question that was asked earlier about direct-to-consumer and the well-informed patient?

The CHAIRMAN. Yes, certainly.

Ms. DAVENPORT-ENNIS. Earlier, the observation was made that patients are extremely well-informed and that they often go to physicians with requests for particular therapies, and I would certainly concur with that. But having said that, I do think we still have a nation that has a digital divide. And while we may have certain patients that get on the Internet and they become very well informed and have a lot of material, we still have citizens that are very dependent upon electronic media to bring to their attention newly-developing products, newly-developing protocols that may be helpful.

I think when we consider the role of direct-to-consumer advertisement, the patient community feels that that process has to be responsible and the ads have to be held accountable for identifying what are the benefits to the drug, what are the risks to the drugs, what specifically can a consumer expect if they are prescribed a drug. And at the end of the day, if they walk into the physician's office with direct-to-consumer information in their hand to say, "Prescribe this for me," at that point, we have a health provider in the country who can be the gatekeeper, who can further educate the patient that, yes, indeed, that is a wise request, or we need to revisit that and look at another option. So I just wanted to point that out to the committee and for the record.

The CHAIRMAN. Thank you very much.

Ms. DAVENPORT-ENNIS. You are welcome.

The CHAIRMAN. Again, of course, I need to mention, then, that people that are doing research on the Internet should not believe everything on the Internet. There are a few rumors going around about Congress out there that are absolutely not true. I would like to make the kind of retirement that they are mentioning that we do, but it is not going to happen and shouldn't happen. But it is a great tool for people to get additional information.

I really thank the panel for all of their answers and their information, and as I mentioned, the record will stay open for another 10 days. The kinds of questions you will get will be far more detailed than what we had here because we try to limit the ones that

might put the audience to sleep but are really essential pieces of information that we need to have to make the kind of decisions we need to do.

I would remind you again that your entire testimony will be part of the record, and if you wish to expand on any of the comments that you had or any of the other questions, we would appreciate that information, as well. Statements by members, their entire statement will also be made a part of the record.

Thank you very much for being here today, and this concludes our hearing.

[Editors Note-Due to the high cost of printing, previously published materials submitted by witnesses may be found in the files of the committee.]

[Additional material follows:]

ADDITIONAL MATERIAL

QUESTIONS OF SENATOR MURRAY

FOR PANEL I—DR. SANDRA KWEDER, DEPUTY DIRECTOR, OFFICE OF NEW DRUGS, FDA

Question 1. As we struggle with the conflicting information surrounding FDA's action regarding Vioxx, I think it is important to understand what current process is in place to ensure that adverse events are promptly reported to the FDA—and that FDA act on these reports.

It is my understanding that Merck shared the FDA clinical trials data that showed an increase of heart attacks and strokes in patients taking Vioxx, as early as 2002. A link showing a higher rate of heart attacks and strokes was evident in ongoing clinical trials.

Did FDA have this information? What prevented FDA from requiring additional warning on the label and advertisements? Why were patients and their doctors kept in the dark about the growing evidence of heart attack and stroke risk associated with the use of Vioxx.

Question 2. Many of us are now looking closely at the post-market approval process. Because it would be almost impossible for FDA to rule out every single risk associated with new drugs and therapies, it is imperative that we have aggressive post-market surveillance. Additional clinical trials can provide more information and risks can be documented over a longer period of time.

Is the FDA Drug Safety process compromised because it is not a separate, independent agency? Why is it important to have the Office of New Drugs involved in the post market surveillance process? And finally, what additional authority or resources does FDA need to meet the current challenges of drug approval and drug safety?

Question 3. Since enactment of PDUFA and FDAMA, there is growing pressure on FDA to eliminate unnecessary delays in new drug approvals. Tight performance standards and requirements could have the appearance of jeopardizing patient safety.

Do you believe that this is true?

Question 4. Does FDA need additional authority to require post-market clinical trials for safety only? Many companies will continue to conduct clinical trials in the hope of achieving FDA on-label approval for a new indication. In fact, Merck continued to study Vioxx to support claims that it reduced GI risks and for treatment of additional diseases like Alzheimer's. It was this process that brought to light the increased risk of heart attack and stroke.

Can FDA, today, order companies to conduct additional clinical trials? Can FDA order a change in a label? Can FDA order a company to withdraw a drug? Does FDA have other steps it can take to alert the public to potential safety concerns, short of a recall?

FOR PANEL II

Question 1. There is a great deal of conflicting information being reported about the FDA and the overall safety of drugs and therapies. Many patients are concerned and are having a hard time evaluating this information. Even looking at the conflicting reports from the FDA Advisory Committee meeting in February, one can understand why patients and their doctors are concerned.

Is the FDA drug approval and safety process broken? How can we restore patient confidence in FDA without reducing timely access to new life-saving drugs?

Question 2. Much has come to light recently about the passive adverse events reporting structure that is currently in place for tracking post-market drug safety. Adverse events are reported to drug companies who then share this information with FDA.

Should we have a more aggressive reporting structure, one which requires physicians to report directly to the FDA? Are there benefits to mining safety data from other databases?

FOR THOMAS FLEMING, PH.D.

Question 3. Again, thank you for your willingness to be here this morning to give all of us the benefit of your 20-plus years of expertise.

In your prepared statement, you mention that in evaluating the effects of Cox-2 inhibitors on the risk of cardiovascular mortality, MI, and stroke, the FDA proceeded in a proper manner regarding the accumulation of data. You also conclude that in general, the FDA has been very effective in carrying out its regulatory re-

sponsibilities and, in turn, has had a strong positive influence on the promotion and protection of public health. These statements appear to conflict with testimony that has been presented to Congress that indicates that the FDA process has not worked and that the agency has not been effective in protecting public health. In fact, there have been allegations of thousands of people suffering heart attacks and strokes because of the failure of the FDA.

Has the FDA process failed? Can we take steps to improve overall public safety without dismantling FDA?

QUESTIONS OF SENATOR CLINTON FOR SANDRA L. KWEDER, M.D.

Question 1. In your testimony, you mention Acting Commissioner Crawford's November 5, 2004 pledge to fill the position of Director at the Office of Drug Safety. Can you please update us on the status of this search?

Question 2. One of the first studies to be performed under the comparative effectiveness provisions of the new Medicare law is a systematic review of the Cox-2 drugs, which will be completed in August 2005. Could you please comment on the ways in which such comparative effectiveness reviews can be used to enhance the work of the Office of Drug Safety?

Question 2a. What expansions and improvements to the comparative effectiveness program would be helpful to the FDA in allowing them to ensure that drugs are safe for all populations?

Question 3. The Pediatric Rule requires companies submitting new drug applications to prove that their products are safe and effective in children before marketing them to the pediatric population. This rule has helped ensure the safety of the drugs prescribed to our children. Are there lessons to be learned from the use of the Pediatric Rule that can be applied to all populations?

Question 4. The FDA is proposing a new Drug Watch webpage that will be used to post emerging information about possible serious side effects for approved drugs. Could you describe in greater detail how information may be disseminated from the Drug Watch website to consumers and providers once potential adverse effects of a drug are noted? How will the voluntary reporting mechanisms of the FDA's current MedWatch system be used to provide data for the Drug Watch website?

Question 5. Would giving the FDA the authority to mandate post-approval monitoring studies improve the ability of the agency to ensure the safety of the drugs available to American consumers?

RESPONSE TO QUESTIONS OF SENATOR ENZI BY SANDRA KWEDER, M.D.

Hon. MIKE ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
Washington, D.C. 20501-6300.

DEAR CHAIRMAN ENZI: Thank you for the facsimiles dated March 21, 2005, including questions for the record related to the Committee's recent hearings, March 1 and 3, 2005, entitled, "FDA's Drug Approval Process: Up to the Challenge?" We have repeated your questions below, followed by the Food and Drug Administration's (FDA or the Agency) response.

Question 1. Could you go into further detail about the interactions between the Office of New Drugs and the Office of Drug Safety? How frequent and in what form are communications during the approval process? During the post-market surveillance process?

Answer 1. The Office of Drug Safety (ODS) and the Office of New Drugs (OND) interact frequently on issues of drug safety for applications under review and marketed products. OND and ODS staff communicate often, both informally and in more formal settings as described below.

ODS includes safety evaluators (clinical pharmacists), epidemiologists (M.D.s and Ph.D.s), medical officers (physicians), health science analysts, project managers, contracts specialists, and database and information technology support in three divisions: the Division of Drug Risk Evaluation (DDRE), the Division of Surveillance, Research, and Communication Support and the Division of Medication Errors and Technical Support.

DDRE's Safety Evaluators are located in the same three buildings as OND review division staff to facilitate communication. DDRE staff have regularly scheduled monthly meetings to discuss pending consults and other safety issues with the Division of Neuropharmacologic Drug Products; bimonthly meetings are held with the Division of Gastrointestinal and Coagulation Drug Products; and DDRE has initi-

ated regular meetings with other OND components including the Division of Reproductive and Urologic Drug Products and the Division of Oncology Drug Products and the Division of Therapeutic Biological Oncology Products.

OND and ODS staff participate in Regulatory Briefings that solicit input from senior Center for Drug Evaluation and Research (CDER) management on regulatory decisions for specific products or classes of products. OND and ODS staff attend a variety of internal meetings. ODS sends representatives to weekly meetings of senior management in OND. ODS and OND management meet bimonthly to discuss topics that affect these offices.

In fiscal year 2004, ODS completed over 1200 reviews of adverse drug reactions, epidemiology studies, medication guides and patient labeling, medication errors, proposed proprietary product names, drug use analyses and database searches. Prior to the initiation of these reviews, during their preparation, and after completion, OND and ODS may informally communicate to define the questions being asked, to provide status information, and contact information, and to explain methodology, content and recommendations for regulatory actions.

ODS staff are involved in the preparation for and may give presentations at advisory committee meetings initiated by OND or ODS involving safety issues and risk management for pending or approved applications and when post-marketing safety information is available for similar products. ODS works closely with the Advisors and Consultants Staff to coordinate the use of the Drug Safety and Risk Management Advisory Committee (DSaRM). DSaRM may meet alone as a full committee, jointly with another CDER advisory committee, or members of DSaRM with relevant expertise may join other CDER advisory committees associated with OND review divisions to provide input on various issues associated with drug safety and risk management.

During the Pre-Market Phase, ODS works with OND before, during, and after pre-new drug application (NDA) and pre-biologics license application (BLA) meetings with industry to review safety information and to discuss proposed risk management plans and the need for any post-approval risk management studies. During NDA and BLA review, ODS and OND work together in the development and review of risk management programs. ODS provides expertise in the review of proposed proprietary drug names, labeling, and packaging to minimize medication errors; in the review of information for patients such as patient labeling and Medication Guides to ensure that product information is communicated clearly and effectively to patients, especially those with lower literacy readability and to ensure adherence to required content and format; and in the review of the need for and the implementation of Phase 4 safety study requirements. OND schedules meetings with ODS called "Pre-Approval Safety Conferences" to discuss safety issues for new chemical entities prior to approval.

During the Post-Market Phase, one of ODS' primary roles is to provide expertise to OND in the review of post-marketing safety data and to maintain and coordinate CDER's post-marketing surveillance and risk assessment program. ODS staff evaluate the safety of marketed drugs through the review of adverse drug event reports submitted voluntarily by consumers and health care professionals through the MedWatch program and required submissions by sponsors of approved NDAs and BLAs. They estimate the public health impact of safety signals and recommend appropriate regulatory actions to OND. They also provide to OND the results of epidemiologic research on drug safety issues, reviews of epidemiologic study protocols and results, and recommendations on risk management programs.

ODS staff are responsible for the acquisition, analysis, and interpretation of information from databases on drug use in various populations, including in-patients, children, and patients over time to which CDER has access under contracts and that help place safety signals into context and inform regulatory decision-making. For newly approved products with important safety concerns, ODS independently evaluates product utilization to evaluate whether these products are being used in a safe manner and works collaboratively and pro-actively with OND and industry on related issues.

ODS reviews reports of medication errors that have occurred with marketed products and recommends changes to product names, labeling, and/or packaging to OND and the Office of Generic Drugs (OGD) to prevent future errors. ODS works with OND and OGD to review risk management programs for approved products to assess their implementation and effectiveness. ODS and OND clinical review staff together develop the scientific basis for labeled warnings, post-marketing safety studies, drug withdrawals and compliance activities.

The Best Pharmaceuticals for Children Act (BPCA) of 2002 mandates that during the first year that a drug receives market exclusivity, any reports of adverse events will be referred to the Office of Pediatric Therapeutics (OPT) and shall be provided

to the Pediatric Advisory Subcommittee. In support of this initiative, ODS staff provides reviews of these adverse event reports to OPT and OND.

Question 2. Merck, the manufacturer of Vioxx, conducted the VIGOR trial to support a new indication for the drug. It is my understanding that the sponsor of a drug application proposes labeling language for new indications. When did Merck first propose new labeling language after the VIGOR trial? How long after the first draft label was received did FDA respond with comments on Merck's proposal? How many rounds of changes did it take to finalize the label?

Answer 2. FDA began discussions with Merck (also referred to as the sponsor) about labeling changes for Vioxx after completing the review of the multiple data sets provided by Merck over the spring and summer of 2001. FDA transmitted changes on October 10, 2001, to the sponsor's original labeling changes submitted as part of NDA 21-042/S007 on June 29, 2000.

The sponsor's response was received on November 6, 2001. Merck's response had little change from the original proposed label that accompanied the NDA supplement submitted in June 2000. A telecon was arranged with the sponsor and Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (DAAODP) explained its position regarding the sponsor's annotations to their counterproposal of November 6, 2001. This telecon took place on November 21, 2001. DAAODP requested that the sponsor reconsider its proposal in light of the division's comments and resubmit the proposal.

Merck submitted a revised response on December 5, 2001. Because there were still substantial differences between the sponsor's and the division's positions, the division presented an update of the labeling discussions regarding cardiovascular (CV) safety at a predecisional meeting at the Center level on January 6, 2002. This venue allows for open discussion of difficult issues with experienced leaders in the Center. There was consensus that the data from the various large databases was of concern and that labeling should include information related to CV findings associated with Vioxx. This was similar to comments made by multiple Committee members at the February 2001 meeting.

FDA transmitted a response to Merck on January 7, 2002. A telecon with Merck took place January 30, 2002. There were still substantial differences between Merck and the division. FDA continued labeling discussions with Merck in teleconferences on February 8 and 20, and March 7 and 20, 2002, until a final label was issued on April 11, 2002.

In April 2002, FDA approved the rheumatoid arthritis indication along with labeling changes that included the results of VIGOR study and changes to the Precautions, Drug Interactions and Dosage and Administration sections of the label to reflect all that was known at the time about the potential risk for CV thrombotic events in Vioxx.

Question 3. Could you describe how staff private-sector experience and financial holdings are reviewed to identify potential conflicts of interest when determining who should be involved in review, approval, and post-market monitoring of a drug?

Answer 3. All employees of FDA are subject to criminal conflict of interest statutes including Title 18, United States Code (U.S.C.) 208, Acts Affecting a Personal Financial Interest, the Standards of Ethical Conduct for Employees of the Executive Branch, and the Supplemental Standards of Conduct for Employees of the Department of Health and Human Services. FDA employees who work on drug reviews at the GS-13 level and higher are generally prohibited from holding stock in a significantly regulated company. Employees who come from the private sector may not work on issues related to their previous employer for a period of 1 year after the employment relationship has ceased. If the required disqualification period Title 5, Code of Federal Regulations (CFR) § 2635.502 has expired, FDA has an unwritten policy on "reviewing one's own work" and would require the employee to be recused from working on the product. FDA's Ethics and Integrity Staff conduct reviews of the financial disclosure reports filed by FDA employees and provide advice on recusal obligations as needed.

Employees not required to file a financial disclosure form (generally administrative positions, and scientific positions GS-12 and lower) may hold up to \$15,000 of stock in a company and participate in a matter affecting that company. This determination is in concert with the regulatory waiver issued by the Office of Government Ethics, CFR 2640. New employees are required to receive a 1-hour ethics orientation. Ethics' New Employee Orientation covers a variety of topics including financial interest restrictions, outside employment, impartiality in performing official duties as well as an overview on the Office of Government Ethics Standards of Ethical Conduct, DHHS Supplemental Standards of Conduct and the Criminal Conflict

of Interest Statutes. Information on FDA's Ethics program is also available on the FDA Ethics website: <http://www.fda.gov/opacom/ethics/>.

Employees are informed of the rules and regulations and are responsible for complying with these rules. The Ethics and Integrity Staff are available to assist employees and their managers when questions arise regarding the ethics requirements.

RESPONSE TO THE QUESTION OF SENATOR GREGG BY SANDRA KWEDER, M.D.

Question. During the hearings, when questioned about whether the FDA needed additional authority to require label or labeling changes on prescription drug products it appeared that Dr. Sandra Kweder and Dr. Janet Woodcock—the FDA witnesses at each of the hearings—responded differently to the question. Does FDA have adequate authority for the drug approval and postmarket surveillance processes? Does FDA need any additional authority to require label or labeling changes on drug products, to require phase IV clinical trials, or to withdraw marketed drug products? Does FDA need any additional authority to ensure the safety and efficacy of new and marketed drugs?

Answer. We do not believe new statutory authority is needed. We will use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues. In most cases, FDA and the sponsor are able to reach agreement on the labeling text fairly quickly (a few weeks). As Dr. Janet Woodcock testified on March 3, 2005, a key factor in labeling changes is that once a label change is made, old labels in paper form are still in distribution and it takes time to get newer labels into circulation. Dr. Woodcock testified that the new strategy of posting drug safety information sooner using the Drug Watch mechanism will help alleviate that factor because it will enable FDA to get information directly to the people who need it in a timely manner.

In addition to the Drug Watch web page, our February 15, 2005, announcement included plans to create a new Drug Safety Oversight Board (DSB) to provide independent oversight and advice on the management of important drug safety issues and to manage the dissemination of certain safety information through FDA's website to health care professionals and patients. For more information on this initiative, please visit: <http://www.fda.gov/oc/factsheets/drugsafety.html>. Also, FDA is intensifying our current efforts to provide the public with the most important information for the safe and effective use of drugs in patient-friendly language. Two tools, Patient Information Sheets and Health care Information Sheets, will allow FDA to deliver emerging safety information to patients and health care providers.

To carry out these enhancements, the Agency's fiscal year 2006 budget request includes an increase of \$5 million for the Office of Drug Safety, bringing total funding to \$22.9 million (a nearly 25 percent increase).

RESPONSE TO QUESTIONS OF SENATOR HATCH BY SANDRA KWEDER, M.D.

Question 1. You stated that it would be helpful for FDA to have a stronger ability to require changes in labeling to address emerging safety issues. Doesn't FDA already have extensive authority to affect labeling changes under the misbranding provisions of the Federal Food, Drug, and Cosmetic Act (FDC Act)? For instance, Section 502(f) of the FDC Act states that a drug is misbranded if its labeling fails to bear "such adequate warnings . . . as are necessary for the protection of users." Likewise, Section 502(j) provides that a drug is misbranded if it is "dangerous to health" when used according to its labeling. Why aren't these provisions adequate to empower FDA to require labeling changes when new safety issues are identified? How would additional authority provide more power than FDA's existing misbranding authority?

Answer 1. You are correct that FDA presently has authority to affect labeling changes under the misbranding provisions of the Federal Food, Drug, and Cosmetic (FD&C) Act. Accordingly, we do not believe new statutory authority is needed. We will use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues.

Further, cooperation between FDA and its regulated industries has proven over the years to be the quickest and most reliable method to remove potentially dangerous products from the market. This method has been successful because it is in everyone's interest to remove unsafe products from the market as soon as possible. Manufacturers carry out most withdrawals of FDA regulated products voluntarily. In some instances, a company makes a discovery that results in initiation of a withdrawal by the company. In other cases, FDA informs a company of new findings and suggests or requests a withdrawal. Usually, the company will comply. FDA encour-

ages health care practitioners and consumers to use drug products as directed in product labeling and within a product's intended population.

Question 2. You also stated that labeling negotiations between FDA and sponsors usually are not a problem. Can you please expand on this statement? How often do sponsors and the FDA agree on labeling changes in a timely manner? In your opinion, are significant delays rare?

Answer 2. Significant delays in labeling negotiations are rare. In most cases, FDA and the sponsor are able to reach agreement on the labeling text fairly quickly (a few weeks). However, in some cases FDA and the sponsor remain far apart on interpretation of the data and proposed labeling text. In those cases it may be necessary to have meetings with the sponsor involving upper level CDER management and/or to seek the advice of an advisory committee.

CDER has established internal review goals of no more than 180 days to complete changes to labeling. In many cases, such as where the change involves the addition of new safety information, the labeling changes may be submitted under FDA regulations as a Changes Being Effected (CBE) Supplement. These regulations allow the sponsor to implement the changes prior to specific FDA review and approval. The prioritization of review of labeling supplements within CDER is based on a variety of factors, but most importantly the significance of the change and the potential impact of the change to furthering the safe and effective use of the drug. Some of the factors that CDER considers include the seriousness of the new information with regard to the health risk posed, the change it represents from the current label, the benefits provided to physicians and patients, the seriousness of the condition the drug is intended to treat, and the number of patients potentially affected. Additionally, the quality of the new safety data may vary from ironclad evidence of a problem to only a subtle suggestion of a signal.

In most cases, the sponsor of the application submits draft text for the new labeling along with supporting data and other information for FDA review. The amount of supporting information can vary from a few pages to many volumes of reports of newly completed analyses of existing or newly completed studies. Following FDA's review of the data, FDA makes any necessary changes to the sponsor's draft labeling text and sends the revised labeling back to the sponsor. Depending on the degree of agreement or disagreement between FDA and the sponsor on the interpretation of the data and the new labeling text, there may be additional rounds of back and forth exchange of draft labeling text.

In all cases, CDER strives to ensure that significant new safety information is communicated to the public as quickly as possible. Sometimes this communication occurs via changes to the labeling and in other cases it occurs through other mechanisms such as Public Health Advisories even while the discussions with the sponsor regarding the final labeling text are proceeding.

As part of its new safety initiatives, FDA is committed to making the process of communicating new safety information about drugs even more transparent and effective, and we have already taken steps to implement those goals such as posting physician and patient information sheets on FDA's website and the issuance of Public Health Advisories.

Question 3. During the March 1, 2005 hearing, Dr. Scott Gottlieb of the American Enterprise Institute stated that the labeling process benefits from a vigorous dialogue between FDA and the drug sponsor. Do you agree that there is value in the process of discussing labeling changes with a sponsor? Dr. Gottlieb also stated that providing additional authority to permit FDA to impose labeling changes on sponsors could result in less effective risk communication because it likely would circumscribe this important dialogue process. Do you agree that this is a risk?

Answer 3. FDA agrees that there is value in the process of discussing labeling changes with a sponsor.

As noted above, we do not believe new statutory authority is needed. We will use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues.

In general, cooperation between FDA and its regulated industries has proven over the years to be the quickest and most reliable method to remove potentially dangerous products from the market. This method has been successful because it is in everyone's interest to remove unsafe products from the market as soon as possible. Manufacturers carry out most withdrawals of FDA regulated products voluntarily. In some instances, a company makes a discovery that results in initiation of a withdrawal by the company. In other cases, FDA informs a company of new findings and suggests or requests a withdrawal. Usually, the company will comply. FDA encour-

ages health care practitioners and consumers to use drug products as directed in product labeling and within a product's intended population.

We cannot speculate whether additional authority would result in less effective risk communication between FDA and sponsors. FDA will continue to work with Congress to ensure it has sufficient authority in drug safety matters, and will continue to work with sponsors to make safe and effective drug products available to those who need them as fast as possible without compromising safety and efficacy.

Question 4. In your testimony you stated that FDA will be implementing a new initiative to ensure that established and emerging drug safety data are quickly available to health care providers and the public in an easily accessible form. In the rare instances where FDA and a sponsor cannot reach agreement in a timely manner on appropriate labeling changes, wouldn't this initiative provide an effective mechanism for FDA to notify health care providers and the public of important new safety concerns with the product in question?

Answer 4. Yes. Simultaneous with FDA's labeling discussions with the manufacturers, FDA strives to inform public health professionals of what is known about safety risks associated with products of concern through public health advisories and updates on FDA's website. FDA's new drug safety initiatives will improve transparency by providing emerging information to health care providers and patients about the risks and benefits of medicines.

Senator Kennedy

RESPONSE TO QUESTIONS OF SENATOR KENNEDY BY SANDRA KWEDER, M.D.

Question 1. In the VIGOR trial, compared with naproxen, Vioxx at 50 mg increased the risk of heart attacks by a factor of 5. At that dose, the approved indication was the short-term treatment of acute pain. Please provide all drafts of the formal or informal FDA risk-benefit analyses that, in the light of the VIGOR results, supported the continued marketing of the 50 mg strength of Vioxx. Do these risk-benefit analyses still seem reasonable to you?

Answer 1. FDA carefully considered all the CV findings from the VIGOR study, and available data from other trials, in assessing the impact of the VIGOR data on the continued safe use of the drug. FDA presented the results of the VIGOR study at a public Arthritis Advisory Committee meeting on February 8, 2001. The GI, CV, and general safety results of the VIGOR study were presented and discussed extensively. The expert panel, which included two cardiologists, recommended that both the positive GI information (reduced risk of serious gastrointestinal bleeding versus naproxen) as well as the potential increased risk of CV events (compared to naproxen) be included in the label. The panel did not recommend withdrawal of the 50 milligrams (mg) dose from the market.

Vioxx 50 mg was originally approved only for the short-term management of acute pain. Based on the data available to FDA at that time, we concluded that the potential risk of short-term use of VIOXX 50 mg did not outweigh the potential benefits. FDA did however, request changes to the VIOXX labeling that were implemented that specifically stated that the prolonged use of the 50 mg dose was not recommended and that the maximum recommended dose for prolonged use in osteoarthritis and rheumatoid arthritis was 25 mg daily.

FDA's analysis of VIOXX was based on our assessment of the available data, the recommendations from the advisory committee, and our best judgment of the potential benefits of the drugs compared to the potential risks of the drug when used according to the recommendations included in the revised labeling.

As you know, FDA convened a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committees in February 2005 to discuss overall benefit to risk considerations, including CV and GI safety concerns for COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs). The Advisory Committees analyzed all available information from recent studies of Vioxx, Celebrex, Bextra, naproxen, and other data for non-selective NSAIDs and COX-2 selective products.

Following the joint meeting, FDA scientists conducted a thorough internal review of the available data regarding CV safety issued for COX-2 selective and non-selective NSAIDs. It was determined that Bextra was associated with an approximately two-fold increased risk of serious CV events compared to placebo. On April 6, 2005, FDA completed a "Decision Memo—Analysis and Recommendations for Agency Action—COX-2 Selective and Non-Selective NSAIDs" based upon the internal review. The Decision Memo stated that, based upon detailed conclusions, the Agency should ask the manufacturer of Bextra, Pfizer Pharmaceuticals, to voluntarily remove Bextra from the U.S. market. Pfizer agreed to do so.

On April 7, 2005, FDA issued the enclosed Public Health Advisory, indicating that the Agency had asked Pfizer to voluntarily remove Bextra from the U.S. market. The Agency is also asking manufacturers of all marketed prescription NSAIDs, including Celebrex (celecoxib) to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of CV events and the well described, serious, potential life-threatening GI bleeding associated with their use.

Further, manufacturers of non-prescription (over-the-counter) NSAIDs are also being asked to revise their labeling to provide more specific information about the potential CV and GI risks of their individual products and remind patients of the limited dose and duration of treatment of these products in accordance with the package instructions. In addition, FDA advised the public to contact their health care providers to see if other marketed NSAIDs may be helpful in treating their pain. For more information on FDA's recent actions, please visit: <http://www.fda.gov/cder/drug/infopage/COX2/default.htm>.

Regarding the Senator's request for "all drafts of the formal or informal FDA risk-benefit analyses that, in the light of the VIGOR results, supported the continued marketing of the 50 mg strength of Vioxx, these were supplied to the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee in connection with their February 2005 meeting where they analyzed all available information from recent studies of non-selective NSAIDs and COX-2 selective drug products." The information is available online at: <http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090b1-01.htm>.

Question 2. Some have estimated that thousands of people suffered fatal heart attacks or strokes because they used Vioxx. You have described these as "theoretical deaths." What did you mean by that statement?

Answer 2. Studies that project the numbers of deaths from adverse drug reactions are usually epidemiological studies. Epidemiology takes certain information that is received and attempts to apply that information to the entire population. Conclusions from this data are not conclusive, but are merely estimates. Any epidemiological study that says a million patients suffered adverse events is a theoretical estimation of the total adverse drug reactions that is derived by extrapolating the actual numbers observed to the population as a whole. Therefore, these can be considered "theoretical" deaths. The accuracy of projection is highly dependant on the accuracy of the information, methodology, and assumptions used in the study. While theoretical deaths are estimates and must be distinguished from confirmed deaths, this nevertheless provides valuable information about potential outcomes, and FDA takes this information very seriously in determining whether to revise the risk/benefit profile for a particular drug.

Question 3. FDA officials have suggested that Dr. David Graham's research on Vioxx was flawed and attempted to delay or block its publication and to undermine his integrity as a scientist.

Answer 3. Dr. Graham was the sole FDA investigator on the study with Kaiser on Vioxx and other drugs. At the time comments were made, other FDA scientists had not been able to review the full study documentation, and thus, independently confirm the scientific assumptions and accuracy of the reported findings. FDA's review had been limited to the final work products provided by Dr. Graham, which included 2 abstracts, a poster presentation, a study report, and a draft manuscript.

Dr. Graham worked with scientists outside of FDA on the Vioxx study on this rather complex epidemiologic design, which included use of statistical scoring to try to compare the sicker patients receiving COX-2 agents to those receiving traditional NSAIDs. Of particular concern to FDA officials was their incidental discovery that in May 2004, Dr. Graham and his collaborators had published findings with the Conference Proceedings of the American College of Rheumatology that were notably different from their findings in August-September 2004. Analysis and review by FDA officials could find no simple or satisfactory explanation for the differences, and so they made their concerns known to Dr. Graham. When Dr. Graham did not address these concerns, FDA officials made them known to the Lancet.

Dr. Graham eventually provided a partial response to FDA concerns about his study, and in that response noted that several analytic and quality control errors had occurred in the conduct of the study. Full explanation or documentation of the Vioxx study still has not occurred. Its reported results continued to vary until its final publication in the Lancet. Major FDA concerns were addressed, and so the study was cleared with an FDA disclaimer. Full FDA endorsement of the study would require the typical rigorous FDA review process of the full study documentation. As detailed elsewhere, FDA scientific review standards often exceed those of

scientific journals? peer review, since FDA requirements capture design limitations, errors, and modifications often unknown to journal reviewers.

By way of background information, Dr. Graham initiated his Vioxx study with supervisory agreement in 2001. In February 2004, Dr. Graham submitted an abstract to the International Society for Pharmacoepidemiology for presentation at the group's August 2004 meeting in Bordeaux, France. The abstract included no results. Dr. Graham submitted his written results and conclusions as a poster presentation to his ODS supervisors for their review and clearance on August 11, 2004. In the course of FDA review and clearance of the proposed poster presentations, several FDA scientists in ODS and OND raised questions about the methods and conclusions in the poster. Like most posters, the proposed poster presented the study methods, results, and conclusions in an abbreviated form and so did not describe the study methodology in a sufficiently complete form to allow others in FDA to review it and determine whether they agreed with its methods and conclusions.

Dr. Graham voluntarily chose to revise his conclusions based on FDA official input and traveled to France to present it. Upon his return, Dr. Graham's ODS supervisors asked him to submit a draft study report detailing his methods and his findings and this was done on September 30, 2004. It was in the review of this study report and accompanying draft manuscript that FDA officials found and raised the concerns described at the beginning of this response.

Question 4. Do you believe that his studies are flawed? If so, how? Don't you believe that publication of research in a peer-reviewed journal, as Dr. Graham was pursuing for his study, is the best process for evaluating the strengths and weaknesses of scientific data?

Answer 4. Again, FDA places great importance on Dr. Graham's work. However, publication in a scientific journal is not always the best process for evaluating the strengths and weakness of scientific data. Over the years, FDA has drawn attention in letters-to-the-editor of scientific journals of selective and favorable publication of study findings where FDA's own review standards (including independent review of primary data according to pre-established study endpoints) showed otherwise. FDA reviewers operate under strict rules pertaining to financial conflict of interest, such that editors of prestigious medical journals have specifically sought FDA reviewers as being the most free of financial and intellectual conflicts of interest.

First, it is a standard practice for FDA employees to have their work peer-reviewed according the Agency's longstanding process. This is critical for reasons of data quality and validity, since no individual can fully and objectively critique his own work. Without peer review, studies risk errors in their methods, findings, and conclusions from overlooked problems and flawed assumptions. Such errors can adversely affect the public health by misleading the scientific and medical communities about safety or efficacy information that is incorrect. Sound science depends on a rigorous peer-review process to ensure that any assumptions and conclusions made are scientifically valid.

In addition, each journal's peer review process is not identical. They vary in the extent of and thoroughness of their expert review. Some journals ask for primary study data to be made available to them, while others do not. Peer reviewers may be misinformed if the data that are shared with them have been "cleaned" or otherwise edited without their knowledge.

Further, FDA is always open to ideas to make its drug safety program even better. Acting Commissioner Lester M. Crawford recently announced a five-step plan to strengthen FDA's drug safety program, including an Institute of Medicine (IOM) study to evaluate the current drug safety system. In an effort to improve the current process immediately, CDER has instituted a program to formally address the opinions of dissenting scientific reviewers to ensure that the decision-making process is transparent. For more information on this plan, please visit: <http://www.fda.gov/bbs/topics/news/2004/NEW01131.html>.

In addition, FDA will enhance the independence of internal deliberations and decisions regarding risk/benefit analyses and consumer safety by creating an independent DSB. The DSB will oversee the management of important drug safety issues within CDER. The DSB will comprise members from FDA and medical experts from other HHS agencies and government departments (e.g., Department of Veterans Affairs) who will be appointed by FDA's Commissioner. The board also will consult with other medical experts and representatives of patient and consumer groups. For more information on this initiative, please visit: <http://www.fda.gov/oc/factsheets/drugsafety.html>. CDER's Manual of Policies and Procedures has been updated to reflect the organization of the DSB; you may view this document by visiting: <http://www.fda.gov/cder/mapp/4151-3.pdf>.

Question 5. You explained in your testimony that FDA is required to disclose to the public its medical and clinical pharmacology reviews of studies conducted under the pediatric exclusivity provision. You also say how rich and valuable this source of information is for pediatricians. Why shouldn't such disclosure be the rule for all drug applications? Why should other patients and their doctors be routinely denied this information, as is the case now?

Answer 5. Outside of the scope of the Best Pharmaceuticals for Children Act, the Agency generally may not publicly disclose information contained in investigational NDAs, unapproved NDAs, or unapproved supplemental NDAs. Only after an NDA or supplemental NDA is approved can the Agency make public certain summary information regarding the safety and effectiveness of the product for the approved indication.

FDA is open to any recommendations that the IOM study may make in this area. In the meantime, the Agency is moving forward with the creating of the "Drug Watch" web page for emerging data and risk information and increased use of consumer-friendly information sheets written especially for health care professionals and patients. These specific proposals, announced on February 15, 2005, by HHS Secretary Mike Leavitt and Acting FDA Commissioner Lester M. Crawford, are immediate and fundamental steps to improve the way FDA manages drug safety information. FDA has recently issued a draft guidance entitled, "FDA's 'Drug Watch' for Emerging Drug Safety Information," which articulates the Agency's current thinking on the topic. This draft guidance is open for public comment and may be viewed by visiting: <http://www.fda.gov/cder/guidance/6657dft.pdf>.

Question 6. You testified that a drug stays on the market if the benefit exceeds the risk its intended use and intended population. Suppose a drug is killing people for an off-label use or outside its intended population. Can the FDA take it off the market?

Answer 6. If a company does not voluntarily withdraw an unsafe product from the market, FDA can pursue a variety of legal action under the Federal Food, Drug, and Cosmetic Act. These legal actions include seizure of available product, and/or injunction of the firm, including a court request for recall of the product. FDA can also initiate administrative proceedings to withdraw the approval of the drug product. Cooperation between FDA and its regulated industries has proven over the years to be the quickest and most reliable method to remove potentially dangerous products from the market. This method has been successful because it is in everyone's interest to remove unsafe products from the market as soon as possible. Manufacturers carry out most withdrawals of FDA regulated products voluntarily. In some instances, a company makes a discovery that results in initiation of a withdrawal by the company. In other cases, FDA informs a company of new findings and suggests or requests a withdrawal. Usually, the company will comply. FDA encourages health care practitioners and consumers to use drug products as directed in product labeling and within a product's intended population.

Question 7. Did the FDA's passive post-market adverse event surveillance system produce any signal that Vioxx or other COX-2 drugs were causing heart attacks or strokes? If not, what enhancements to post-market surveillance are needed?

Answer 7. During early surveillance after marketing, the Division of Drug Risk Evaluation within CDER's Office of Drug Safety examined the passive surveillance system several times looking for adverse events of heart attacks or strokes associated with COX-2 agents. None of these reviews was able to convincingly discern whether these adverse outcomes were likely related to COX-2 use. This inconclusiveness is due to an inherent limitation of passive surveillance systems in detecting an elevation in the risk of a commonly occurring adverse event such as a heart attack or stroke.

Passive surveillance systems are incomplete in the number and nature of the reports they receive. As a consequence, only unusual or distinctive drug-related adverse events stand out as safety signals (e.g., liver failure, Torsade de Pointes (TdP), Stevens Johnson syndrome.)

Expansion or refinements to FDA's adverse event reporting system are unlikely to help the system discern whether a relatively common condition or outcome with other probable causes such as heart attack or stroke is caused by a drug. Individual case reports cannot reliably answer such a question unless the person is distinctively free of risk factors for the adverse event in question.

Determining if the risk of a common event is elevated by a drug product with long term use is probably best assessed by population-based studies, where people receiving the drug are compared to a similar group of individuals who have not received the drug. The best population-based studies of this type would be randomized clini-

cal trials, where patients of similar illness and risk factors are randomly assigned either to drug treatment or placebo. Observational epidemiologic population studies are much more difficult to conduct and interpret since people who are prescribed drugs are often sicker and have more risk factors than people who do not receive drugs. This is called confounding by indication. Complex statistical corrections (also known as controlling for differences) are done in an attempt to make the comparisons fairer. This can be difficult in some cases, such as in the Kaiser study where the patients who were prescribed COX-2 agents had many more risk factors for CV disease at the outset than the people who were not prescribed these drugs. Such a baseline imbalance makes interpreting epidemiologic analyses difficult.

Question 8. You stated that any person who experienced reduced pain while using Vioxx benefited from using the drug. Do you also think that it was safe for them to take it?

Answer 8. "Safe" is not an absolute term when discussing drugs. All drugs have risks. A physician who prescribed Vioxx should have been knowledgeable about drugs risks and benefits so as to make the best choice of therapy for a patient. FDA takes very seriously its role in making sure that the official labeling for a drug reflects all that is known about the benefit/risk profile of the medication.

FDA worked diligently to change the Vioxx label after the VIGOR study results. In September 2004, after Merck's withdrawal of Vioxx from the market, FDA issued a Public Health Advisory stating that the risk that an individual patient taking Vioxx will suffer a heart attack or stroke related to the drug is very small but noting that patients who are currently taking Vioxx should contact their physician for guidance regarding discontinuation and alternative therapies.

In December 2004, the Agency issued another Public Health Advisory following recently released data from controlled clinical trials showing that the COX-2 selective agents (Vioxx, Celebrex, and Bextra) may be associated with an increased risk of serious CV events (heart attack and stroke) especially when they are used for long periods of time or in very high risk settings (immediately after heart surgery). In this Public Health Advisory, FDA noted that physicians prescribing Celebrex (celecoxib) or Bextra (valdecoxib), should consider this emerging information when weighing the benefits against risks for individual patients, that patients who are at a high risk of GI bleeding, have a history of intolerance to non-selective NSAIDs, or are not doing well on non-selective NSAIDs may be appropriate candidates for COX-2 selective agents, and that individual patient risk for CV events and other risks commonly associated with NSAIDs should be taken into account for each prescribing situation.

Most recently, following the joint meeting of FDA's Arthritis and Drug Safety and Risk Management Advisory Committees, Agency scientists conducted a thorough internal review of the available data regarding CV safety issued for COX-2 selective and non-selective NSAIDs. It was determined that Bextra was associated with an approximately two-fold increased risk of serious CV events compared to placebo. On April 6, 2005, the FDA issued a "Decision Memo—Analysis and Recommendations for Agency Action—COX-2 Selective and Non-Selective NSAIDs" (copy enclosed) based upon the internal review. The Decision Memo stated that, based upon detailed conclusions, the Agency should ask the manufacturer of Bextra, Pfizer Pharmaceuticals, to voluntarily remove Bextra from the U.S. market. Further, the Decision Memo stated that if Pfizer did not agree to remove Bextra from the U.S. market, FDA would initiate the formal withdrawal procedures.

On April 7, 2005, FDA issued the enclosed Public Health Advisory, indicating that the Agency had asked Pfizer to voluntarily remove Bextra from the U.S. market. The Agency is also asking manufacturers of all marketed prescription NSAIDs, including Celebrex (celecoxib) to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of CV events and the well described, serious, potential life-threatening GI bleeding associated with their use. Pfizer has suspended marketing of Bextra at this time.

Further, manufacturers of non-prescription (over-the-counter) NSAIDs are also being asked to revise their labeling to provide more specific information about the potential CV and GI risks of their individual products and remind patients of the limited dose and duration of treatment of these products in accordance with the package instructions. In addition, FDA advised the public to contact their health care provider to see if other marketed NSAIDs may be helpful in treating their pain. For more information on FDA's recent actions, please visit: <http://www.fda.gov/cder/drug/infopage/COX2/default.htm>.

Sincerely,

PATRICK RONAN,
Assistant Commissioner for Legislation.

RESPONSE TO QUESTIONS OF SENATOR ENZI BY NANCY DAVENPORT-ENNIS

Question 1. In light of recent controversies, some people have proposed requiring longer-term and larger studies of drugs before they are approved. Could you comment on whether and how this might impact patients?

Answer 1. Time is a highly precious commodity to someone diagnosed with a life altering and/or life threatening condition like cancer, AIDS, or diabetes. The diagnosis not only impact the patient, but also their families, friends and communities. When you are suffering from a potentially fatal or severely debilitating disease, you shouldn't have to wait any longer than is necessary for the FDA to approve new medical products. Any attempt to mandate longer or larger clinical trials would obviously increase the length of time before patients would have access to new products if they are deemed safe and effective. When you are suffering and dying, the risk/benefit ratio is significantly different than in patient populations in other circumstances.

The process for the review of new drugs draws upon the most complete and appropriate medical evidence collected through carefully-controlled clinical trials, the expert judgment of FDA staff, and the advice of patients and doctors on the advisory committees. Approval comes down to decisions about how much risk and uncertainty should be tolerated and, in turn, depends on the strength of the evidence on the benefits that a new drug or device will provide. The invariable feature of drug development is that no matter how extensive or carefully designed the pre-approval clinical trials, a full understanding of benefit and risk is possible only after millions of patients have been treated, often times, for many years.

Such decisions about the size and length of a trial should continue to be conducted on a case-by-case basis by scientific and medical experts who are the most qualified and best equipped to make decisions about the design of clinical trials and who have experience that may be very similar. That is not to say that in some cases, a longer and/or larger clinical trial might be appropriate for the proper evaluation of a proposed product's safety and efficacy, even if that means a potentially longer waiting period for patients. For example, a longer trial may be necessary in order to detect delayed toxicities. A larger number of trial participants may be necessary in order to detect very uncommon toxicities. However, this decision should be determined on a case-by-case basis by the clinical trial Institutional Review Board (IRB).

However, in many cases, smaller and/or shorter clinical trials may be sufficient for the rigorous evaluation of a new product.. Because the appropriate clinical trial design may vary greatly depending on the specific human testing proposed and what the testing is intended to demonstrate, imposing a uniform requirement that all clinical trials should include a greater number of subjects or extend for a greater length of time would not be scientifically grounded. IRBs in both hospital and clinical settings have historically been charged with answering those questions.

Our preliminary background research on the matter revealed that current FDA regulations provide conceptual parameters for different phases of trials (i.e., Phases 1, 2, and 3), but they do not specify a standard number of subjects in, or lengths of time for, clinical trials to support a new drug application. Companies are required to justify the size and length of study in their clinical protocol, which is submitted to FDA prior to initiation of the study as well as through the IRB that will monitor and track clinical trial status. FDA does not require a particular number of

patients or length of follow-up. Rather, the appropriate sample size is derived strictly from statistical calculations, and the length of follow-up is dependent on the safety and efficacy endpoints being measured. We believe these standards are sufficient to ensure that both safety and efficacy can be proven.

FDA recommends that applicants follow the "Guidance for Industry: Good Clinical Practice" in developing clinical studies.¹ This Guidance was developed in conjunction with the International Conference on Harmonization ("ICH"), and provides unified standards applicable to studies intended to generate clinical data for submission to regulatory authorities in the United States, European Union, and Japan, thus socializing data from country to country for enhanced reporting of clinical trial activities and results.

The exciting news for present and future patients is that scientific discovery, particularly in emerging fields such as genomics and proteomics, is laying the foundation for an ability to effectively gauge safety and efficacy through smaller and perhaps shorter clinical trials. For example, diagnostic tools are being developed that will allow physicians to identify those patients with a particular type of cancer or those who are likely to develop a particular type of cancer, and then match those

¹ FDA/ICH "Guidance for Industry: Good Clinical Practice: Consolidated Guidance" (April 1996) available at <http://www.fda.gov/cder/guidance/959fnl.pdf>.

patients with the best available treatment or preventive option for that specific cancer. This technology might also dramatically improve the safety of trials as well.

FDA is taking new steps to develop better information about pharmacogenomics—the differences in the way people respond to drugs and the types and dosages of medications from which they are most likely to benefit and least likely to suffer an adverse event. The application of this knowledge will provide the ability to screen patients for their level of susceptibility to certain side effects, which will help physicians determine in advance which clinical trials and/or treatment options may be the most appropriate in terms of balancing safety and efficacy. (There is a recent example of this in the approval of the Roche AmpliChip Cytochrome P450 Genotyping test; please see <http://www.fda.gov/cdrh/mda/docs/k042259.html>).

Thus, science is rapidly developing a capacity to identify the best candidates for particular clinical trials from both a safety perspective and an efficacy perspective, which in many cases would provide an opportunity to conduct smarter, shorter, smaller, and safer clinical trials. With the emergence of this technology already on the horizon, a requirement for longer and larger clinical trials could prevent one of the most useful applications of such advancements. Consequently, such requirements could unnecessarily expose patients to greater risk for longer periods of time and unnecessarily impose additional burdens in terms of time and resources on those who design and conduct clinical trials.

The length and size of the clinical trial is one of the most expensive aspects of the research and development process. According to recent industry estimates published by Cutting Edge Information, the average per-patient cost of a Phase I trial is about \$5,500; the average for a Phase II trial is \$6,500; and the average Phase III trial costs more than \$7,600 per patient. A widely cited study on drug development costs conducted by Tufts University estimates that the average per patient cost to conduct clinical trials is \$23,572. The National Cancer Institute (NCI) estimated that its average per patient cost for a clinical trial ranged from \$3,861 to \$6,202 (depending upon the year) for the DCP Cooperative Group Treatment Trials conducted between 1993 and 1999.

Any mandate for larger and longer clinical trials would dramatically increase the overall cost of research and development. Such increases could have a chilling effect on the pace of scientific discovery.

Fortunately, the continued development of new, scientifically based capacities to enable shorter, smaller, and smarter clinical trials holds great promise for dramatically reducing the skyrocketing costs associated with the clinical trials component of research and development. Since the cost of conducting a clinical trial sometimes prevents companies from pursuing promising new products (particularly those that would be used only in certain patient sub-populations), any technological advancements that reduce the cost of clinical trials could provide a heretofore lacking economic incentive to expand the scope and scale of the research and development pipeline to include new products for diseases and conditions that would otherwise be considered too great of a financial risk. For many patients with limited to no treatment options for their particular disease, a robust research and development pipeline offers them and future patients the best hope for potential improvements in their quality of life and/or life expectancy.

Question 2. Many have called for a greater separation between the Office of New Drugs, which is responsible for drug approvals, and the Office of Drug Safety, which is responsible for post-market surveillance of drugs that have already been approved. Are you concerned that an independent Office of Drug Safety would only look at risks and problems, potentially ignoring the benefits?

Answer 2. Patients and their families, physicians and caregivers must always weigh the benefits and risks associated with a particular treatment option. Similarly, we feel that the FDA must carefully weigh the benefits and risks associated with a new drug when making decisions about approval or post marketing activity.

Safety and efficacy are the inseparable foundation of the FDA's ability to best define the appropriate risk/benefit ratio of a product. Risk cannot be considered separately from benefit, nor safety from efficacy. To review one without an equal measure of the other could easily lead to misjudgments and false conclusions. For that reason, we would advise against any effort that creates new regulations or bureaucracy that isolates or further separates the drug safety function from the overall drug review and monitoring process.

Rather than an independent drug safety office operating in isolation, we would prefer strengthening of the existing Office of Drug Safety so it can do a better job in a more timely fashion. Adding new levels of bureaucracy at FDA that only consider safety without consideration for efficacy will almost certainly discourage research on new therapies for deadly diseases like cancer and AIDS. Assuming they

could even be approved, it could be difficult to keep new treatments for these diseases on the market if the regulatory hurdles for safety are too high because those drugs are likely to have some level of side effects, and they are likely to be used in patient populations that are sick and vulnerable to adverse reactions.

Of even greater concern is how an overemphasis on safety might have a devastating impact on the advancements being made in our ability to detect deadly diseases early or prevent them altogether. The conundrum is that the clinical testing and medical application of new technologies for early detection and prevention will involve people at risk for the specific disease who are not yet showing signs of advanced disease and may be entirely without symptoms. However, the tools for early detection and prevention are likely to have side effects, just like any medical intervention.

If the regulatory emphasis on safety is too great, it will be very difficult to get new tools for the treatment, prevention and early detection approved and then keep them on the market even though they may save hundreds of thousands, if not millions, of lives in the not too distant future. Such potential uncertainty can easily discourage the public and private sectors from investing hundreds of millions of dollars into the research and development of new products in this country if those products are likely to face intense scrutiny over safety concerns regardless of their benefits. We can evaluate the number of off-shore clinical trials toady, as opposed to 5 years ago, and see that many US clinical trials have been moved to foreign locations. The patients of the United States would benefit greatly from additional clinical trials taking part in our country.

It always has been an unfortunate but unavoidable fact that some adverse effects may not become apparent until after a drug has been in wide or extended use. We can hope to minimize such adverse effects and enhance the agency's capacity to report them, but we must also accept certain risks associated with beneficial drug products.

With that in mind, we do feel strongly that the FDA can do a better job with its post marketing surveillance activity. We applaud Dr. Lester Crawford's announcement that FDA will enhance the independence of internal deliberations and decisions regarding risk/ benefit analyses and consumer safety by creating an independent Drug Safety Oversight Board (DSB). The DSB will oversee the management of important drug safety issues within the Center for Drug Evaluation and Research (CDER). The DSB will comprise members from the FDA and medical experts from other HHS agencies and government departments (e.g., Department of Veterans Affairs) who will be appointed by the FDA Commissioner. The board also will consult with other medical experts and representatives of patient and consumer groups.

Another important initiative is for FDA to continue to increase the transparency of its decision-making process by establishing new and expanding existing communication channels to provide targeted and timely drug safety and efficacy information to the public. These channels can be used to help ensure that established and emerging drug safety and efficacy data are quickly available in an easily accessible form to those who will bear the risks: patients and their caregivers. The increased openness will enable patients and their healthcare professionals to make better-informed decisions about individual treatment options. To address these objectives, the FDA must stress efficient risk management—finding the least costly approach to achieving the most risk reduction for patients. Efficient risk management requires using the best scientific data, quality standards, and efficient systems and practices that provide clear and consistent decisions and communications for the public and regulated industry. Although we see it only as a first step, we are pleased that the Agency is proposing a new "Drug Watch" Web page for emerging data and risk information and increased use of consumer-friendly information sheets written especially for healthcare professionals and patients. Finally, we believe FDA will need to employ more user-friendly, automated adverse event reporting systems.

In order to achieve these objectives, we strongly believe additional financial resources will be required. Moreover, without new resources, every dollar the FDA shifts towards new regulations and infrastructure for safety is money taken away from programs that allow the agency to more effectively and efficiently evaluate risk and benefit together in the New Drug Approval process.

RESPONSE TO QUESTIONS OF SENATOR ENZI BY THOMAS R. FLEMING, PH.D.

Question 1. What are some of the strengths and limitations of "observational" or longitudinal studies versus placebo-controlled studies? Is it appropriate to pull a drug from the market based solely on observational studies without some sort of active control?

Answer 1. In the post-marketing setting, multiple sources of information are useful in monitoring for safety signals. Recalling my testimony on March 1, 2005, these sources include:

“(i) post-marketing passive surveillance, such as is provided by the Adverse Event Reporting System (AERS); (ii) post-marketing active surveillance, such as is provided by large linked data bases, in particular for products that will have wide spread use; and (iii) post-marketing randomized trials to rule out unacceptable increases in the rate of clinically significant safety risks that are uncommon or occur on a delayed basis, when evidence has been obtained to suggest the plausibility of such risks.”

The first two sources are “observational” studies. The strengths of these passive and active surveillance methods are their ability in some settings to provide timely detection of safety signals for products as used in real world settings. These approaches are especially useful when there is a strong temporal relationship, (i.e., the safety risks occur immediately after the administration of the product), when there are biological factors supporting plausibility of risk, and when the intervention induces a very large increase in the relative risk of safety events that otherwise would have occurred very rarely in clinical practice, (e.g., detecting the association of intussusception with use of the rotavirus vaccine, or Stephens-Johnson rash with use of an HIV/AIDS drug, or ruling out an association of encephalitis with use of an acellular pertussis vaccine).

These sources of information provided a sufficient basis to remove the rotavirus vaccine from the market, because this vaccine did induce a large and temporally related increase in the rate of the usually rare event of intussusception. More often, however, due to important limitations in these passive and active surveillance “observational” studies, such sources of information are more useful for hypothesis generation regarding safety signals, where such hypotheses then need to be rigorously assessed using post-marketing randomized trials. This is particularly true when the intervention provides a moderate increase in the risk of a clinically significant safety event, especially if this increase might occur on a delayed basis. The identification of the increased risk of cardiovascular (CV) death, MI and stroke, caused by use of Cox-2 inhibitors, is a classic example of this situation. Recalling my testimony on March 1, 2005 about limitations of passive and active surveillance sources of evidence regarding detection of safety signals:

Due to lack of a randomized control group, frequently unavailable confounder information (such as aspirin use or smoking history when studying Cox-2 inhibitors), concerns regarding outcome specificity (are reported events truly events?) and sensitivity (are true events reliably captured?) partly due to recall bias, and concerns resulting from loss to follow-up and the lack of a proper “time zero” cohort, results from these analyses can be very misleading, especially when one is attempting to determine whether an intervention induces a clinically important safety risk that corresponds to less than a 2-fold increase in rate of occurrence of these safety events. These concerns appear to be relevant to the setting of Cox-2 inhibitors. While their effect on the risk of CV deaths, MI and stroke is clinically significant, it appears that this effect is approximately at the level of a 1.5 fold increase, an important but not dramatic increase. In such settings, the FDA properly would view such “epidemiological” or “observational” evidence, with all its limitations, to be hypothesis generating or clues regarding safety signals. The FDA properly recognized that it was necessary to conduct post-marketing randomized trials, with large sample sizes and long term follow-up, to reliably address the CV safety risk of the Cox-2 inhibitor class, so that risks could be reliably weighed against the proven benefits.

This testimony also gave several examples to illustrate that more reliable large post-marketing randomized clinical trials often provide substantially different conclusions from observational studies regarding the frequency and severity of safety risks. Results from observational trials usually should be viewed with caution, in the spirit of hypothesis generation, and usually should not serve as the sole basis to justify removing a drug from the market.

Question 2. Your testimony includes some very interesting statistics as to the size of a clinical trial that would have to be conducted to pick up adverse events of a given frequency. It's all well and good to say that a risk is equal to a “1.2 fold increase over background,” but that doesn't mean much to most people. Do you have any thoughts on how to best communicate to doctors and patients the absolute and relative risks of side effects?

Answer 2. While one useful approach to summarizing the magnitude of a safety signal is to report the estimated increase in relative risk, such as a “1.2 fold increase over background”, you correctly note that additional ways of conveying risk are very helpful to patients and care givers. For example, the “CV mortality, MI and stroke” safety signals for Cox-2 inhibitors have been evaluated in a large number of completed randomized clinical trials involving more than 75,000 patients. The proportion of patients in the control arms of these trials who experienced the outcome of “cardiovascular death, MI and stroke” was approximately 1 percent (i.e., 10 per 1,000 patients) per year. (This proportion was smaller in settings such as rheumatoid arthritis and larger in settings such as Alzheimer’s disease and coronary artery surgery). In such instances where the background rate is 1 percent, if a drug induces a 1.5 fold increase in the risk of “CV death, MI and stroke”, it might be helpful to recognize that this indicates the drug causes 5 additional “CV mortality, MI, and stroke” events per 1000 patients treated, increasing the expected number of events from 10/1000 to 15/1000 per year. (If the background rate were 2 percent per year, a 1.5 fold increase would correspond to increasing the expected number of events from 20/1000 to 30/1000 per year). This risk then needs to be considered in the context of the totality of information about the benefit-to-risk profile of the intervention.

RESPONSE TO THE QUESTION OF SENATOR KENNEDY BY THOMAS R. FLEMING, PH.D.

Question. In the VIGOR trial, compared with naproxen, Vioxx at 50 mg increased the risk of heart attacks by a factor of 5. At that dose, the approved indication was the short-term treatment of acute pain. Do you believe there is a benefit to 50 mg of Vioxx over other treatment options that outweighs this risk?

Answer. Data from clinical trials evaluating several Cox-2 inhibitors in a variety of clinical settings and doses strongly suggest that these agents, as a class, increase the risk of CV death, MI and stroke. This evidence is particularly strong for Vioxx at evaluated doses of 25mg and 50mg. From the 8000 patient Vigor trial, it is estimated that patients receiving the 50 mg dose of Vioxx have approximately 2.4 times the risk of these irreversible morbidity/mortality events. Due to “regression to the mean” or to use of lower doses, validation trials involving an additional 15,000 patients have indicated that the true level of increased risk of these events is likely smaller (probably closer to a relative risk of 1.5). Nevertheless, this increased risk in treatment induced mortality and irreversible morbidity is more clinically significant than the beneficial reduction in the risk of significant upper GI ulcers provided by Vioxx relative to non-selective NSAIDS. Given that Vioxx has not been established to provide improved pain relief relative to non-selective NSAIDS such as naproxen, the totality of available information does not suggest that Vioxx, at evaluated doses, provides a benefit-to-risk profile that is favorable relative to that of non-selective NSAIDS.

There is anecdotal evidence suggesting that Vioxx might provide substantial benefit to some patients with significant pain who have not obtained relief from other treatment options. Such evidence could motivate conducting randomized trials that would compare the relative pain relief provided by Vioxx versus standard-of-care, in a cohort of patients who have not received benefit from multiple regimens involving non-selective NSAIDS. It might be possible to establish that Vioxx has a favorable benefit-to-risk profile relative to other treatment options in this restricted clinical setting if such trials were conducted and yielded strongly positive results regarding the ability of Vioxx to provide significantly superior pain relief relative to these other treatment options, in particular if these efficacy results were to be achieved using lower doses of Vioxx that could be shown to induce smaller increases in the risk of CV death, MI and stroke.

While future trials might establish that certain doses of Vioxx have a favorable benefit-to-risk profile relative to other treatment options in some restricted clinical settings, marketing of a product should be based on what has been, rather than what might be, established. Currently available data have established that Vioxx induces serious safety risks and have not shown that it provides advantages over available treatment options where these advantages are of comparable or greater clinical significance than the induced safety risks. Hence, on the February 16-18 2005, while serving on the FDA Advisory Committee reviewing safety of Cox-2 inhibitors, I voted “No” to the question, “Does the overall risk versus benefit profile for rofecoxib support marketing in the United States?”

RESPONSE TO QUESTIONS OF SENATOR ENZI BY DAVID FASSLER, M.D.

AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY,
WASHINGTON, D.C. 20016,

April 1, 2005.

Hon. MICHAEL ENZI,
*Chairman,
 Committee on Health, Education, Labor, and Pensions,
 U.S. Senate,
 Washington, DC. 20510.*

DEAR CHAIRMAN ENZI: Thank you for your inquiries regarding the U.S. Food and Drug Administration drug approval process following my testifying at the H.E.L.P. Committee hearing you convened March 1, 2005. I am pleased to provide the following response to your questions.

Question 1. You have supported the call for additional large-scale research studies on both the safety and efficacy of all of the SSRI medications. These are clearly post-market studies. Do you support larger scale and/or longer pre-approval studies on drugs that may be used in children and adolescents?

Answer 1. Many of the clinical trials currently conducted in conjunction with the approval of a new medication are relatively short-term. However, children and adolescents often take medication for an extended period of time. Both the American Psychiatric Association (APA) and the American Academy of Child and Adolescent Psychiatry (AACAP) support both larger scale and longer studies on the safety and efficacy of medications used in the treatment of pediatric patients. Such studies should be conducted both prior to and after approval. Data from these trials should also be included in a centralized registry, accessible to the general public. Physicians and parents need and deserve access to such information in order to make appropriate decisions regarding treatment options.

Question 2. The British Medicines and Healthcare Products Regulatory Agency and the American FDA took different actions to modify the use of SSRI anti-depressants in children and adolescents. The British agency limited NHS prescribers to one SSRI only, Prozac. FDA went with a label change. Can you compare and contrast these two approaches. In your professional opinion, what is the impact of these two approaches on treating depressed children and adolescents?

Answer 2. The British regulators correctly concluded that the Food and Drug Administration has more information regarding the use of fluoxetine in the treatment of pediatric patients. However, the general clinical consensus in this country is that the SSRI antidepressants are roughly equivalent in terms of overall safety and efficacy. The selection of a specific medication is influenced by a number of factors including the side effect profile (e.g., effects on sleep, appetite, etc.), pharmacological properties (e.g., the half-life of the medication), and previous history with a specific medication, including positive or negative experience among other family members. Research indicates that approximately 60 percent of children and adolescents with depression will respond to an initial medication. However, many of the remaining 40 percent will respond to a second, or sometimes even a third medication. Prohibiting prescribing of medicines for those 40 percent of pediatric patients can hinder effective treatment of mental illnesses. For this reason, physicians need continued access to the full range of possible treatment interventions.

With respect to the SSRI antidepressants, several large scale ongoing studies are currently underway which will significantly enhance our knowledge regarding the use of these medications in children and adolescents. These include TADS (Treatment for Adolescents with Depression Study), TASA (Treatment of Adolescent Suicide Attempters), and TORDIA (Treatment Of Resistant Depression In Adolescents). The results of these studies will help us refine our ability to determine which children and adolescents are most likely to respond to a specific intervention.

Question 3. One of the problems pediatric researchers face are the small number of patients available for study. That is particularly important where a side effect may be identical in appearance to the natural history of the disease, such as in depression. Do you think that these problems impacted FDA's actions with respect to the SSRIs? How could we improve FDA's ability to respond?

Answer 3. It is particularly challenging to evaluate potential side effects which are similar or even identical to symptoms associated with an underlying illness. FDA made an attempt at this challenge with respect to the SSRI antidepressants. In its process, FDA may not have fully considered the side effect profiles and the psychopharmacologic profiles of the antidepressants on its studies' patients. This observation underscores the importance of ensuring that the FDA has access to, and

queries, researchers and clinicians with appropriate background and expertise to assist regulators in distinguishing between side effects and underlying symptoms. In particular, I have suggested the development of a Pediatric Central Nervous System Advisory Committee which could provide such input, as necessary, to improve FDA's ability to respond.

Thank you again for the opportunity to share with the Committee my professional and experiential opinions. On behalf of the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry, I look forward to working with you in the future on these critical pediatric psychiatry matters.

Sincerely,

DAVID FASSLER, M.D.

RESPONSE TO QUESTIONS OF SENATOR ENZI BY ABBEY S. MEYERS

NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD),
DANBURY, CT, 06813-1968,
March 24, 2005.

Hon. MICHAEL B. ENZI,
Chairman,
Health, Education, Labor, and Pensions Committee,
Washington, DC. 20510.

DEAR MR. CHAIRMAN: Thank you for the two questions regarding my testimony at the drug safety hearing of the HELP Committee. My answers are as follows:

Question 1. As you know, there are things about rare disorders that make a different approval standard appropriate. Could you discuss whether rare disorders are the right model for approval for drugs to treat more common disorders, and if so, how that model would translate?

Answer 1. The *Orphan Drug Act of 1983* does not provide a different standard for orphan drug approvals. During 3 years of intense debate about the design of the law, consumers made it very clear that we wanted orphan drugs to comply with the same standards of safety and efficacy as other pharmaceuticals and biologics. We do not want treatments that are less safe, or less effective than other treatments. Rather, the law provides financial incentives to entice companies into developing drugs for small populations of patients (fewer than 200,000 patients in the United States), because the industry felt that such small populations represent a limited market that would not be profitable enough. However, the law does provide a mechanism for patients to have access to orphan drugs while they are still investigational if the patient is not eligible to participate in a controlled clinical trial. In this case the patient gives informed consent and the doctor provides the medicine under an IND.

At the beginning of the AIDS/HIV epidemic FDA was under pressure to speed the development of new AIDS drugs, but consumers representing other deadly diseases felt that the rules should not be changed for one disease. Rather, the new rules should allow an accelerated approval process for treatments applicable to any serious or life-threatening disease when other treatments were unavailable or unsatisfactory. Subsequently, then Commissioner Frank Young created an "accelerated approval" or a "fast-track" process allowing drugs for serious and/or life-threatening diseases to show less efficacy data than is required for drugs to treat less serious conditions, or serious conditions where there were already available therapies. However, the manufacturer had to promise to conduct clinical trials (to confirm the efficacy or treatment benefit) after the drug was on the market.

Section 506 of the Food and Drug Modernization Act of 1997, which codifies the regulation instituted in the 1980s by Commissioner Young, defines fast-track as follows:

Designation of Drug as a Fast Track Product.—In general. The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition. (In this section, such a drug is referred to as a "fast track product".)

Thus, since the mid-1980s until now, drugs for many diseases, both rare and common, were eligible to use this process if the drug fit within the serious or life-threatening parameters of the regulation. However, the drug had to have concrete clinical evidence that it was probably safe and effective before it could be approved for patients under the fast track system, and manufacturers had to promise they would

conduct these confirmatory post-approval (Phase 4) trials if the FDA asked them to. As you know, not all of those Phase 4 trials have been done, and those that have been done may have taken longer than FDA required.

Question 2. Ms. Meyers, you have testified previously that the primary purpose of the FDA Modernization Act “was to speed the approval of more new drugs and devices, even if those drugs and devices were relatively unimportant to the public health.” But we know that no two drug compounds are exactly the same in terms of how they affect patients. Each patient has a unique genetic predisposition that affects how a drug affects him or her. Each patient has his or her related or unrelated medical complications that affect how a drug reacts. A drug that might be right for me, might not be right for you—so who decides which drugs are important or not important to the public health?

Answer 2. There has been much written about “personalized medicines”, but they are not yet available for general use. This is primarily because science does not yet have the tools to understand the genetic differences between humans. The first DNA test to examine how a person’s liver may metabolize certain drugs has very recently been approved by the FDA, and some cancer drugs can be aimed at certain types of tumors but not others. Everyone expects that science will evolve so that personalized medicines will eventually become available in the future, but it is not available now, and doctors generally cannot prescribe a treatment based on a person’s genetic profile.

It is indeed true that a drug that works for me may not be good for you. Companies spend a lot of money developing “me-too” drugs for common diseases that are similar to other available therapies (e.g., many companies have or were recently developing Cox-2 inhibitors for the most common form of arthritis, osteoarthritis). There are minor differences between these drugs in order not to violate a competitor’s patent. But in terms of speeding approval of any new drug, FDA should recognize that arthritis is not life-threatening, there are dozens of available treatments already on the market for arthritis pain, and the people who take pain drugs are either healthy people who want minimal risk from any medication (e.g., for a sprained ankle or dental pain), or elderly people with other diagnoses who are taking other drugs. The risk of a dangerous interaction with other medicines, the difference of metabolism between young healthy patients and older people, and the problems of taking a medicine long-term for a chronic disease like arthritis, should raise significant safety questions before a new drug for arthritis pain enters the market.

The only way for a doctor to tell which drug will work better on a person with arthritis is to prescribe each one, one at a time. The manufacturers of Vioxx and Celebrex have never claimed that their products are more effective than other anti-inflammatories. In general they were marketed to be “as effective”, but with greater safety on the stomach. However, there are other anti-inflammatories on the market that are manufactured to dissolve in the intestines rather than the stomach, for patients who have stomach problems. Additionally, long-term studies of the Cox-2 inhibitors have shown that people who took the drugs for more than one year had an equal incidence of stomach ulcers to those who took older anti-inflammatories.

So I agree with you, Senator Enzi, that “me-too” drugs that are similar to other medications, are good because they provide more choice for consumers, even though doctors are usually unable to determine which may be better for each patient. But these kinds of treatments for non-life threatening diseases, that will be taken chronically for a disorder such as arthritis, and used by a frail elderly population with other illnesses, should not be approved for marketing on a priority review. Instead such drugs should be studied longer on a population that reflects the “real world” market, not a pristine group of individuals who have no other complicating factors. Once these drugs reach our local pharmacies, people with heart conditions, diabetes, high cholesterol, etc., take them. Even if FDA thought that the first Cox-2 inhibitor was a break-through drug, then the second and third Cox-2 drugs should not have been reviewed on a shortened priority basis.

We believe that fast-track reviews of pharmaceuticals should revert to their original intent: They should be used as treatments for serious and life-threatening diseases that have no other satisfactory treatments available (an unmet medical need).

I hope this answers your questions.

ABBEY S. MEYERS,
President, National Organization
for Rare Disorders (NORD).

RESPONSE TO QUESTIONS OF SENATOR ENZI BY WILLIAM B. SCHULTZ

Question 1. You have proposed giving the FDA the authority and responsibility to limit how doctors can prescribe medicine for their patients. Each patient's situation is different, and I'm concerned that a regulatory agency that weighs risks and benefits of a drug on a population level is ill-equipped to make those decisions on a personal level. Once a drug has been approved by the FDA, isn't it best left to doctors and patients to make decisions about the risks and benefits?

Answer 1. I am not proposing that FDA be given authority to direct how physicians treat individual patients. Unfortunately, however, there are examples of where physicians simply do not pay attention to the FDA-approved label. Since we, as a Nation, have given FDA the responsibility to review available data and to analyze the risks and benefits of drugs (a task which few physicians or patients are qualified to undertake, even if they had the time), in limited circumstances FDA should have authority to ensure that physicians follow the Agency's directions. One possibility is to give FDA the authority to limit certain drugs to specific medical specialties. The Agency already has this authority for medical devices. The other possibility would be to give FDA explicit legal authority to place limitations on the use of particular drugs (such as where a drug can be used safely only in connection with a certain test or where certain uses are clearly unsafe). I do not know whether this last option is viable, but I offer it for consideration.

Question 2. Many have called for a greater separation between the Office of New Drugs, which is responsible for drug approvals, and the Office of Drug Safety, which is responsible for post-market surveillance of drugs that have already been approved. Are you concerned that a separate Office of Drug Safety would only look at risks and problems, potentially ignoring the benefits?

Answer 2. I think that it is important that the expertise of the Office of New Drugs be used in assessing safety problems that are identified after a drug is approved. Whomever is given the responsibility for deciding whether to limit the use of a drug or to withdraw the drug must be directed to consider both risks and benefits, just as FDA must consider both risks and benefits when deciding whether to approve a drug.

Question 3. You suggest that FDA does not have clear statutory authority to require a postmarket study, but it appears that FDA successfully gets postmarket study commitments. In fact, the vast majority of drug approvals (73 percent) between 1998 and 2003 included a postmarket study commitment. Can you comment on how FDA is able to get postmarket study commitments from drug sponsors in these cases even though it may not have clear statutory authority?

Answer 3. You are correct that prior to approval FDA sometimes obtains commitments from companies to conduct postmarket studies. However, as the case of Vioxx demonstrates, after a drug is approved, it is often essential to obtain additional information, and at that time the agency has no leverage or authority to obtain postmarket commitments. My understanding is that the agency does not often (if ever) seek or obtain commitments to undertake postmarket studies after a drug has been approved. In my opinion, FDA should be given legal authority to require companies to conduct postmarket studies where new information raises questions about a drug after it has been approved.

Even at the time of approval, with no legal authority, the Agency has inadequate leverage to obtain commitments to conduct the necessary postmarket studies. And even when commitments are made, it has no authority to require companies to fulfill their commitments. At various times, it has been estimated that drug companies do not meet a significant percentage of their commitments to conduct postmarket studies. Legal authority to require postmarket studies would allow FDA to negotiate adequate studies at the time the drug is approved and to enforce the postmarket study commitments that it obtains from companies.

[Whereupon, at 11:43 a.m., the committee was adjourned.]

